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SAHPRA POLICY ON CONDUCT OF CLINICAL TRIALS OF HEALTH PRODUCTS DURING THE CURRENT COVID-19 PANDEMIC[1]

[1]Adapted from: FDA's Guidance on Conduct of Clinical Trials of Medicinal Products During the COVID-19 Pandemic (18 March 2020)

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1. Introduction

The South African Health Products Regulatory Authority (SAHPRA) is committed to providing timely health products regulatory guidance in support of continuity for stakeholders and appropriate timely regulatory response during the current COVID-19 pandemic. Specifically, this communication provides assistance to sponsors and applicants including clinical research organizations (CROs) in assuring the safety of trial participants, maintaining compliance with current good clinical practice (GCP), and minimising risks to trial integrity during the COVID-19 pandemic.

2. Background

There is currently an outbreak of respiratory disease caused by a novel coronavirus that was first detected in Wuhan City, Hubei Province, China, and that has now been detected in many locations internationally, including cases in South Africa. The virus has been named "SARSCoV-2" and the disease it causes has been named "Coronavirus Disease 2019" (COVID-19).

SAHPRA recognizes that the COVID-19 pandemic may impact the conduct of clinical trials of health products. Challenges may arise, for example, from quarantines, site closures, travel limitations, interruptions to the supply chain for the investigational and other trial related products or other considerations, if site personnel or trial subjects become infected with COVID-19.

These challenges may lead to difficulties in meeting protocol-specified procedures, including administering or using the investigational product or adhering to protocol-mandated visits and laboratory/diagnostic testing. SAHPRA recognizes that protocol modifications may be required, and that there may be unavoidable protocol deviations due to COVID-19 illness and/or COVID-19 control measures.

Although the necessity for, and impact of, COVID-19 control measures on clinical trials will vary depending on many factors, including the nature of the disease under study, the trial design, and in what region(s) the study is being conducted, SAHPRA recommends the following measures to assist sponsors in assuring the safety of trial participants and research staff, maintaining compliance with current good clinical practice (GCP), and minimizing risks to trial integrity.

3. Discussion

3.1 Ongoing trials:

i. **Safety of trial participants:** Sponsors should consider each circumstance, focusing on the potential impact on the safety of trial participants, and modify study conduct accordingly. Study decisions may include those concerned with:

a. Continuing trial recruitment;
b. Continuing use of the investigational, as well as concomitant and comparative products for patients already participating in the trial;
c. The need to amend patient monitoring SOPs in the trial

ii. **Safety precautions for trial staff:** Principal Investigators and site personnel have a critical role in the conduct of Clinical Trials and assuring safety of trial participants. The sponsors, applicants, clinical research organizations and principal investigators should adhere to the National Department of Health and World Health Organization guidelines on measures to control transmission of COVID-19.

iii. **In-study Informed Consent:** In all cases, it is critical that trial participants are kept informed of amendments to the study protocol and any monitoring plans that could impact them. Sponsors, in consultation with Principal Investigators, including National Principal Investigators, and Research Ethics Committees, may determine that the protection of a participant's safety, welfare, and rights is best served by continuing a study participant in the trial as per the protocol or by discontinuing the administration or use of investigational or other products or even participation in the trial. Such decisions will depend on specific circumstances, including the nature of the investigational and other products, the ability to conduct appropriate safety monitoring, the potential impact on the investigational and other products supply chains, and the nature of the disease under study in the trial.

iv. **Impact of social distancing measures on study logistics:** Since trial participants may not be able to come to the investigational site for protocol-specified visits, sponsors should evaluate whether alternative methods for safety assessments (e.g. telephone contact, virtual visit, alternative location for assessment, including local laboratories or imaging facilities) could be implemented when necessary and feasible, and would be sufficient to assure data integrity and safety of participants.

Sponsors should determine if in-person visits are necessary to fully assure the safety of trial participants (for example to carry out procedures necessary to assess safety or the safe use of the investigational product appropriately); in making the decision to continue use or administration of the investigational or other products, both the sponsor and principal investigator(s) should consider whether the safety of trial participants can be assured with the implementation of the amended monitoring approach.

v. **Impact of social distancing measures on participant monitoring:** In some cases, trial participants who no longer have access to the investigational or other products, or to the investigational site, may need additional safety monitoring (e.g. withdrawal of an active investigational treatment). If planned on-site monitoring visits are no longer possible, sponsors should consider optimizing use of central and remote monitoring programmes to maintain oversight of clinical sites.

vi. **In-study protocol amendments:** The need to put new processes in place or to modify existing processes will vary by the protocol and local situation. For example, this assessment could include consideration of whether it is appropriate to delay some assessments for ongoing trials, or, if the study cannot be properly conducted under the existing protocol, whether to stop ongoing recruitment, or even withdraw ongoing trial participants.

COVID-19 screening procedures that may be mandated by the healthcare system in which a clinical trial is being conducted do not need to be reported as an amendment to the protocol, even if done during clinical study visits, unless the sponsor is incorporating the data collected as part of a new research objective.

Sponsors and principal investigators are encouraged to consider alternative approaches or changes to the protocol or investigational plan to minimize or eliminate immediate hazards or to protect the life and well-being of research participants (e.g. to limit exposure to COVID-19). Protocol amendments should typically not be implemented before review and approval by SAHPRA and relevant ethics committees.

Protocol amendments occasioned by COVID-19 may include:

a. Changes that will have minimal impact on participants. For such changes, applicants should notify SAHPRA and proceed; and

b. Protocol Amendments that have potential to affect the safety of participants and trial integrity. In such cases, applicants should submit the protocol amendments to SAHPRA for approval before proceeding.

vii. **Record of in-study protocol deviations:** SAHPRA encourages sponsors and principal investigators to work with their Research Ethics Committees to prospectively define procedures to prioritize reporting of deviations that may impact the safety of trial participants. The implementation of alternative processes should be consistent with the protocol to the maximum extent possible, and sponsors and principal investigators should document the reason for any contingency measures implemented.

Sponsors and Principal Investigators should document how restrictions related to COVID-19 led to the changes in the study conduct and the duration of those changes. It should also be indicated which trial participants were impacted, and how those trial participants were impacted.

viii. **Impact of social distancing measures on data collection:** Changes in study visit schedules, missed visits, or patient discontinuations may lead to missing information (e.g. for protocol-specified procedures). It will be important to capture specific information in the case report form (CRF) that explains the basis of the missing data, including the relationship to COVID-19 for missing protocol-specified information (e.g. from missed study visits or study discontinuations due to COVID-19). This information, summarised in the clinical study report, will be helpful to both the sponsor and SAHPRA.

ix. **Impact of social distancing measures on investigational and other products administration:** If scheduled visits at clinical sites will be significantly impacted, certain investigational and other products, such as those that are typically distributed for self-administration, may be amenable to alternative secure delivery methods. For investigational and other products that are normally administered in a health care setting, consulting SAHPRA on plans for alternative administration (e.g. home nursing or alternative sites by trained but non-study personnel) is recommended. In all cases, existing regulatory requirements for maintaining investigational and other product accountability remain and should be addressed and documented.

x. **Impact of social distancing measures on assessment of study endpoints:** With respect to efficacy assessments, SAHPRA recommends consultation with the Clinical Trials Unit regarding protocol modifications for the collection of efficacy endpoints, such as use of virtual assessments, delays in assessments, and alternative collection of research-specific specimens, if feasible. For individual instances where efficacy endpoints are not collected, the reasons for failing to obtain the efficacy assessment should be documented (e.g. identifying the specific limitation imposed by COVID-19 leading to the inability to perform the protocol-specified assessment).

xi. **Impact of in-study protocol deviations on data management:** If changes in the protocol will lead to amending data management and/or statistical analysis plans, the sponsor should consider doing so in consultation with the Clinical Trials Unit. Prior to locking the database, sponsors should address in the statistical analysis plan how protocol deviations related to COVID-19 will be handled for the pre-specified analyses.

3.2. Where policies and procedures are not already in place to deal with the impact of COVID-19 on clinical trials:

i. Sponsors, Principal Investigators, and Research Ethics Committees should consider establishing and implementing policy and procedures, or revise existing policy and procedures, to describe approaches to be used to protect trial participants and manage study conduct during possible disruption of the study as a result of COVID-19 control measures at study sites.

ii. Changes to policy and procedures could address, but not be limited to, impact on the informed consent process, study visits and procedures, data collection, study monitoring, adverse event reporting, and changes in investigator(s), site staff, and/or monitor(s) secondary to travel restrictions, quarantine measures, or COVID-19 illness itself. Policy and procedures should be compliant with current disaster management measures and policy for the management and control of COVID-19.

iii. Protocol amendments should typically not be implemented before review and approval by SAHPRA.

3.3 FOR TRIALS THAT ARE ALREADY BEING IMPACTED BY THE COVID-19 PANDEMIC:

i. Sponsors should describe in appropriate sections of the clinical study report (or in a separate study-specific document):

a. Contingency measures implemented to manage study conduct during disruption of the study as a result of COVID-19 control measures;

b. A listing of all participants affected by the COVID-19 related study disruption by unique subject number identifier and by investigational site, and a description of how the individual's participation was altered; and

c. Analyses and corresponding discussions that address the impact of implemented contingency measures (e.g. trial participant discontinuation from investigational or other products and/or study, alternative procedures used to collect critical safety and/or efficacy data) on the safety and efficacy results reported for the study.

Robust efforts by sponsors, principal investigators, and Research Ethics Committees to maintain the safety of trial participants and study data integrity are expected, and such efforts should be documented. As stated above, SAHPRA recognizes that protocol modifications may be required, including unavoidable protocol deviations due to COVID-19 illness and/or COVID-19 control measures. Efforts to minimize impacts on trial integrity, and to document the reasons for protocol deviations will be important.

3.4 Submission of Documents during Lockdown following COVID-19 Pandemic

The SAHPRA reception will remain closed during the lockdown and correspondence should be emailed to the dedicated email addresses mentioned below:

- E-mail address for Responses to new Clinical Trial applications and related queries: ctcresponses@sahpra.org.za
- E-mail address for Protocol amendments, responses to amendments and related queries: ctcamendments@sahpra.org.za
- E-mail address for Additional Investigators & Sites, responses to additional and related queries: ctcinvestigators@sahpra.org.za
- E-mail address for Bioequivalence studies, BE amendments, responses to BE studies and related queries: ctcbeprotocols@sahpra.org.za
- E-mail address for Notifications and related queries: ctcnotifications@sahpra.org.za
- E-mail address for Individual Patient Serious Adverse Events and related queries: ctcsaes@sahpra.org.za
- Email address for clinical trials conduct guidelines and related queries: ctcguidelines@sahpra.org.za

For further questions on clinical trial conduct during the COVID 19 pandemic, please email Ms Kedibone Malatji (kedibone.malatji@sahpra.org.za) or Ms Dominicah Thosago (dominicah.thosago@sahpra.org.za).