



**MINISTRY OF HEALTH
PHARMACY AND POISONS BOARD**

**GUIDANCE TO SPONSORS AND INVESTIGATORS FOR CONDUCT OF
CLINICAL TRIALS DURING THE COVID-19 PANDEMIC
IN KENYA**

April 2020

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| PPB/MIP/CT/GUD/023 | Guidance to Sponsors and Investigators for Conduct of Clinical Trials During the COVID-19 Pandemic in Kenya | Revision No. 0 | Effective Date 20 th April 2020 |
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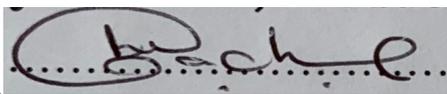
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Prepared by Quality Assurance Officer

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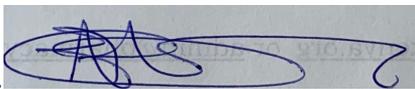
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Reviewed by Director, Product Safety

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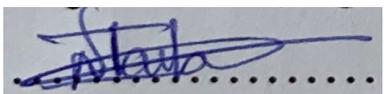
Date.....15th April 2020.....

Reviewed by Deputy Director General, Medical Products and Health Technologies

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Date.....15th April 2020.....

Checked by Head, Quality Management

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Date.....15th April 2020.....

Authorized by Chief Executive Officer

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Date.....15th April 2020.....

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Abbreviations and Acronyms

| | |
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| COVID-19 | Coronavirus Disease 2019 |
| EMA | European Medicines Agency |
| MHRA | Medicines and Healthcare Products Regulatory Agency |
| MOH | Ministry of Health |
| PPB | Pharmacy and Poisons Board |
| TGA | Therapeutic Goods Administration, Australia |
| WHO | World Health Organization |
| ICH GCP | International Conference on Harmonization Good Clinical Practice. |

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Foreword

The COVID-19 pandemic has brought about disruptions in the day to day activities across the world. This has had a great impact on the conduct of clinical trials and therefore calls for establishment of measures to protect the safety and wellbeing of clinical trials participants and staff. In addition, contingency measures need to be put in place to ensure the integrity of the results of the trials going on.

As the country currently has a number of clinical trials approved and taking place, it is hoped that this guidance will be helpful to the clinical trials study teams and sponsors.

Kenya is an important centre for the conduct of clinical trials and as the National Medicines Regulatory authority of Kenya, PPB will continue to facilitate clinical trials by ensuring that all clinical trials are scientifically sound, ethical and are conducted as per International Conference on Harmonization on Good Clinical Practice (ICH GCP).

As the pandemic continues, and scientific data and information continues to grow and become clear, the Pharmacy and Poisons Board will continuously monitor the situation and update this guidance.

The PPB will collaborate with other national, regional and international partners to facilitate the conduct of clinical trials at this critical time, and also after the end of the COVID-19 pandemic.

This guidance has therefore been made to assist sponsors and investigators as they carry out their clinical trials during this pandemic outbreak time. It should be used together with the other existing guidelines.

Finally, as key stakeholders in the conduct of clinical trials, please feel free to submit your feedback on this guidance that we shall be reviewing as we get more information as the COVID -19 pandemic.



Dr F. M Siyoi

CEO, Pharmacy and Poisons Board

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Legal Framework

The regulation for the conduct of clinical trials is governed under the provisions of the Pharmacy and Poisons Act, Cap 244 Laws of Kenya (hereinafter referred to as the “Act”) and the Subsidiary Legislation thereunder.

Under the provisions of Section 2 of the Health Laws (Amendment) Act, 2019 (hereinafter referred to as “the Health Laws (Amendment)”) which amended the Act, Clinical Trial is defined as, any systematic study on pharmaceutical products in human subjects, whether in patients or other volunteers, in order to discover or verify the effects of, identify any adverse reacting to investigational products, to study the absorption, distribution, metabolism and excretion of the products with the object of ascertaining their efficacy and safety.

The Board is statutorily empowered to undertake various duties in execution of her mandate regarding regulation of medicines. With respect to Clinical Trials, the Board is empowered amongst others under Section 3 of the Health Laws (Amendment) to;

- (b) Grant or withdraw authorization for conducting clinical trials of medical products
 - (i) Constitute technical and expert advisory committees
 - (o) Approve the use of any unregistered medicinal substance for purposes of clinical trials and compassionate use
 - (p) Approve and regulate clinical trials on medicinal substances
 - (r) Collaborate with other national, regional and international institutions on medicinal substances regulation.

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VISION

To be a leader in promoting and protecting public health

MISION

To protect and promote the health of the public by regulating the profession of pharmacy and ensuring access to quality, safe efficacious and affordable health products and technologies

CORE VALUES

Commitment to Public health, Professionalism, Accountability and Transparency, Integrity and Respect, Quality and. Diversity and inclusion

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Introduction

The novel coronavirus named “SARS CoV-2” has caused a worldwide outbreak of respiratory disease called “Coronavirus Disease 2019” (COVID-19) that has greatly affected the way the world operates. The outbreak led World Health Organization (WHO) to declare the novel coronavirus (COVID-19) outbreak a global pandemic on 11th March 2020.

There is noticeable disruption of clinical trials conduct due to the pandemic owing to the preventive measures put in place including the Presidential and Ministry of Health directives on social distancing, staying at home and restricted inter-county travel . in addition, there is increased demand on health services provision leading to the reallocation of some of the clinical trials staff, coupled with the need of self-isolation by some of the trial participants. These factors are likely to impact on the oversight resulting into a negative impact on the initiation of new trials, difficulties in maintaining a medical oversight of the studies by the investigators , completion of trial assessments , completion of trial follow-up visits and the provision of Investigational Medicinal Products (IMPs).

The COVID-19 pandemic has brought challenges to the conduct and oversight of clinical trials. This is especially so with the Presidential and Ministry of Health directive on social distancing, staying at home and restricted inter-county travel. There is also increased demands on the health service and changes to trial staff availability. Participants may also be required to self-isolate, which introduces difficulties for Investigators to maintain their medical oversight. These challenges could have an impact on the conduct of trials, such as the completion of trial assessments, completion of trial follow-up visits and the provision of Investigational Medicinal Products (IMPs).

The impact of COVID-19 on ongoing trials, on opening a new trial site in an existing trial, ongoing recruitment and continued involvement of

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participants in the trial, or on starting of new trials should be considered. This evaluation should take into consideration the Kenyan Government recommendations and restrictive measures including travel restrictions and confinements of trial participants and trial staff and the availability of trial staff to perform visits, enter data in the Case Report Form (CRF), notify serious adverse events and, more generally, follow the protocol.

Our response to the COVID-19 challenge should be in line with several key principles and considerations. These are:

- Compliance with the latest Presidential and Ministry of Health’s Directives on COVID-19 pandemic
- The safety and well-being of patients, research participants and their families, and health care professionals, researchers and other staff involved in patient care and research are paramount.
- It is critical that public health systems remain able to respond to the needs of the community, both those impacted by COVID-19 and in terms of regular workloads.
- The conduct of research related to COVID-19 is a significant priority; however, the initiation and continuation of other ongoing and proposed research should also be critical for the well-being of patients, participants, communities and the research sector.
- Compliance with or adherence to regulations, guidelines, codes, policies and other standards remains necessary. However, interpretation of research responsibilities in the context of a crisis such as COVID-19 should be informed by flexibility, consultation and good sense so as to retain the focus on the safety and well-being of those most at risk in our institutions and communities.
- Possibilities of invalidating outcomes of on-going studies as a result of confounders due to COVID-19 and associated factors.
- Reference to international guidance from e.g. FDA, EMA, MHRA, TGA (but local/national government guidance is supreme)

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Purpose and scope

This guideline provides general information and advice to researchers and sponsors in the context of the COVID-19 pandemic. It is directed towards those involved in clinical trial and other relevant clinical research. This guidance provides general information and advice to institutions conducting or overseeing research, researchers and sponsors in the context of the COVID-19 pandemic.

The purpose of this guideline is

- Assist those overseeing, conducting and reviewing clinical trial research to maximize the safety of research participants and to minimize risks to participants and the community, to researchers and also ensure the integrity of the clinical trials.

Compliance with or adherence to regulations, guidelines, codes, policies and other standards remains necessary. That said, interpretation of research responsibilities in the context of the current crisis should be informed by flexibility, consultation and good sense so as to retain the focus on the safety and well-being of those most at risk in the institutions and communities.

All submissions to PPB shall be through the online clinical trials portal, www.ctr.pharmacyboardkenya.org and through the email; cta@pharmacyboardkenya.org

In addition, sponsors and researchers can get in touch through Telephone [**+254 709 770 100**](tel:+254709770100)

Ongoing management of current clinical trials

Contingency planning

Institutions, individual principal investigators (PIs) and sponsors should undertake continuous contingency planning to address the potential

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impact of COVID-19 and responses to the crisis on current, ongoing clinical trials. The planning should include:

- **Priority:** assessment of the importance of and the risks associated with continuing the trial as designed or with necessary modifications. Responses could include continuing the trial in its present form, conducting the trial in a modified form, suspending the trial or closing the trial.
- **Participation:** assessment of the ability of participants to participate in the trial in accordance with protocol requirements and consideration of alternative models for participation that would not compromise the integrity of the trial.
- **Capacity:** assessment of the resources available for continuing the trial, including research staff, clinical support staff, pharmacy support, other support staff, space, equipment, supplies, etc.

Contingency planning should be an ongoing process as the pandemic progresses.

Communications

Decisions and actions in response to the crisis will be most effective if they are taken after appropriate consultation with the key stakeholders in a clinical trial: institutions, researchers, sponsors, regulators and, in some cases, participants. However, the need for rapid responses may require decisions and actions by one or more parties without prior consultation with the others. In such cases, all key stakeholders should be informed of the decisions and actions taken at the earliest opportunity.

The Pharmacy and Poisons Board will be readily available to evaluate any urgent amendments.

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Participants

- The safety and well-being of trial participants, other patients, family members, researchers and other clinical and support staff is paramount.
- Study clinics should institute measures to minimize transmission of COVID-19 e.g. ensuring that all staff and participants wear masks and other PPEs, maintain social distance in waiting areas, provide facilities for hand washing or sanitizers.
- In trials that proceed without modification, participants should explicitly be given the following options:
 - a) continuing to participate in the trial
 - b) suspending their participation, if this is viable, or
 - c) withdrawing from the trial.
- Participants who do not attend clinic visits or complete other trial activities may be reminded that these are required; however, if a patient declines or actively refuses to participate in trial activities, then their decision should be respected and they should be considered to have withdrawn from the trial. These participants should be informed that their decision will not affect their ongoing treatment or participation in future clinical trials.
- Participants who choose to move off the investigational product and onto standard care, and who do not wish to continue with site visits may be able to remain on trial for follow-up only.
- Participants should be informed of any modifications to the trial, including medical and other trial procedures, ongoing treatment or care and any tests or assessments that will have, or have the potential to have, an impact on them.
- In trials that have been modified, participants should explicitly be given the following options:
 - a) participating in the trial, as modified, inclusive of alternative mechanisms for engagement such as remote visits, data collection, monitoring, etc., as appropriate
 - b) suspending their participation, if this is viable, or

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- c) withdrawing from the trial.
- Participants should be informed of the importance of notifying the research team in advance of attending any trial visits if
 - a) they are experiencing one or more symptoms suggestive of COVID-19 infection
 - b) they have recently (within 14 days) returned from overseas or have been in close contact with someone who is known to have contracted COVID-19 or
 - c) has symptoms suggestive of COVID-19 infection, or
 - d) they are experiencing one or more symptoms not suggestive of COVID-19 infection, but suggestive of influenza or other infectious disease or condition that includes respiratory symptoms.
 - e) Adverse events reporting by the participants should be emphasised if they have been provided with study agents. This should include both the expected and unexpected adverse effects.
 - f) In addition, research sites may screen all participants by using targeted observation and temperature taking using contactless thermometers before each study visit
- In a situation where a trial participant is unable to attend a visit or otherwise fulfil a condition of participation due to public health directives or government policy (such as restricted travel), sponsors and researchers are encouraged to facilitate the participant being able to continue to participate in the trial at a site that is within the limits of any such restrictions. Data collected could then be transmitted to the site that the participant would normally have attended.
- There should be access to water, soap, sanitizers, social distance, mask, gloves and PPE etc for participant visits at home, clinic or inpatient so as to minimize transmission.
- Participant rights must not be violated and all protections should be accorded to them during the emergency.

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- Sites should report social harms in an expedited manner during this period e.g. violence to participants as a result of study participation.
- If participants need to travel to and from study site, study team need to
 - a) Liaise with relevant authorities to facilitate movement,
 - b) Reconsider mode of transport so that participants are not exposed to unnecessary risks,
 - c) Reconsider layout in the facility to minimise contacts
- Researchers need to go further to protect themselves and study participants in terms of the minimum required social distance especially given that aerosols have been shown to travel further than 6 feet. The study teams need to reassess the layouts of the study areas to be convinced that study areas are safe environments.
- Research sites must adequately dispose of waste related to the study.

The ability to confirm eligibility and to conduct key safety assessments and trial evaluation is of particular importance. Actions to be taken should be proportionate and based on benefit-risk considerations. Where a trial participant is unable to attend the site, other measures, such as home nursing, if possible given social distancing needs, or contact via phone or any other means, may be required to identify adverse events and ensure continuous medical care and oversight. However, the limitations and risks of such methods and the requirements for data protection should be taken into account and such alternative arrangements need to be adequately documented.

The conduct of ongoing clinical trials is critical for the well-being of patients, participants, communities and the research sector.

The PPB will be as flexible and pragmatic as possible with regard to regulatory requirements for clinical trials during this time. We recognize that clinical trial resources may be absent or redeployed from research activities and regulatory affairs towards front-line care.

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The first priority should be the safety of trial participants and this will remain our focus.

This guideline will be updated as the situation changes over time.

Amendments to existing studies

The submission to amendments that require PPB's approval should be done through email; cta@pharmacyboardkenya.org

To support the review, compliance to **section 23** of the current guideline is complied with. In particular, the following information should be included in the submission

- The changes and local implications are made clear
- Any changes to documentation are provided in tracked changes
- Summary of the proposed amendments
- Reason(s) for the amendment
- Impact of the amendment on the original study objectives
- Impact of the amendments on the study endpoints and data generated.
- Impact of the proposed amendments on the safety and wellbeing of study participants

Safety of patients is a priority. If the safety of a participant is at risk because they cannot complete key safety checks, then consideration to discontinuing that participant must be considered. Where necessary, urgent safety measures may be implemented first and notified subsequently.

Amendments to clinical trial protocols that include the addition to an existing trial of new COVID-19 related elements, e.g. to enable epidemiological analysis of COVID-19, to add patients with COVID to an existing trial of a treatment or to add in testing for SARS-CoV-2 for safety

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purposes, (for example where studies include taking samples), is acceptable, so long as appropriate protection is put in place for handling of samples. Such arrangements would be treated as an urgent safety measure with subsequent notification in accordance with usual processes. Use of a separate specific information sheet and consent form to provide information about additional tests rather than modifying an existing form should be considered.

The Pharmacy and Poisons Board will be readily available to evaluate any urgent amendments.

Change to site monitoring arrangements, to reduce burden or physical contact with sites

Remote monitoring visits are encouraged as the first option. These arrangements must adhere to patient confidentiality protocols already in place. Remote source data verification may be done electronically as long as appropriate security arrangements either are or can be put in place.

Any change to remote monitoring must not result in confidential patient information being sent to the sponsor if this has not already been addressed in the participant information sheet. Trial participants will need to consent to any identifiers leaving the site and be assured that their confidentiality will be protected

Source data verification may be done remotely by electronic means if the necessary security arrangements can be put in place, if the arrangements are in line with the participant information sheet.

Sponsors should consider what monitoring needs to be done in real time, and what checks can be undertaken later, taking a risk-based approach.

Where a change to access to confidential patient information will arise as a result of changes to remote monitoring, the revised participant information

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sheet and consent form, along with the risk assessment justifying the changes to access to confidential patient information, should be submitted as a substantial amendment.

The use of alternative means of oversight such as teleconferences/videoconferences is encouraged.

If remote monitoring visits are not feasible, then clinical research associates may continue to undertake on-site monitoring visits as long as they are not symptomatic, have not returned from overseas in the last 14 days or had contact with a known case of COVID-19, in accordance with the most current government and public health guidance.

Investigator meetings

Investigator meetings and other meetings to plan, conduct or monitor a clinical trial should employ the use of remote technology wherever possible. Where researchers are temporarily co-located for the purposes of the delivery of clinical care or the conduct of the trial, engaging in any necessary interaction may be efficient, but should be subject to current public health advice.

Studies making changes to how or when patients are seen to avoid exposing patients

- a) In some cases changes will be deemed by the sponsor to reduce risk of potential exposure to COVID-19 by participants, for example changing participant site visits to phone calls or postal questionnaires. These should be implemented at sites on the date specified by the sponsor after a notification and acknowledgement of the same is received from PPB.
- b) In some cases changes will be deemed by the sponsor to potentially increase risk to participants, e.g. less frequent participant checks. These should be handled as a **substantial amendment**. These should be implemented after getting PPB's review and approval.

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Studies where treatment or investigational medicinal product need to be sent by courier direct to participants or other alternative mechanisms of provision

Sponsors must assess the risks relating to the product and consider any shipping and storage arrangements.

Participants must consent verbally to providing contact details for shipping purposes.

Where participants are self-isolating or in quarantine, arrangements for a nominated person to collect product may be implemented with the participant’s verbal consent. Any such temporary arrangements should be handled as a **non-substantial amendment** that does not require PPB’s approval. A notification of the same shall be submitted to PPB.

Studies where sponsors need to implement a temporary halt to all or some of the study or extend the duration of a study due to COVID-19.

Sponsors must decide when they need to implement a formal temporary halt.

Reporting to PPB for a formal halt is required if there are safety considerations for existing participants, or actions that sites need to take.

Simply pausing recruitment does not need to be reported as a temporary halt, although sponsors should notify PPB.

Studies that need to be closed

For any studies involving provision of treatment to participants, careful consideration should be given to post-study care.

If this cannot be in line with the information provided in the participant-information sheet, a **substantial amendment** should be submitted for review and approval.

End of study report should subsequently be provided.

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Changes instigated by individual sites due to clinical requirements

Sites may need to make rapid changes to manage clinical situations. The priority should be the safety of patients.

Any protocol deviations to be documented.

Studies where sites need to suspend recruitment

Sites must raise such issues with the sponsor as early as possible if this is likely to occur.

A notification on the suspension of recruitment shall be submitted to PPB for acknowledgement.

It is for the sponsor to decide whether or not to temporarily halt or close a study.

Studies where sites need to withdraw participants

For any studies involving provision of treatment to participants, careful consideration should be given to post-study care. If this cannot be in line with the information provided in the participant-information sheet, a substantial amendment should be submitted.

Submitting paperwork for trials which have been halted

If your trial has been halted due to issues related to COVID-19, you will need to inform PPB.

The trial master file should include a note that the trial was halted and the reason.

If a halt is due to either of the below scenarios however, you will need to inform PPB:

- A direct participant safety issue, especially if there is the potential to impact other trials; please inform us in the normal way

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- Medicines supply issue. Inform us of this directly by phone or email rather than an amendment form

Restarting a trial after it has been halted

If the restart of the study does not involve any substantial changes to the initially approved application, then a substantial amendment notification to PPB will not be necessary but an notification should be submitted. If changes do need to be made to protect participant safety moving forward, then this should be submitted as a substantial amendment.

Providing investigational medicinal product (IMP) to trial participants

If a trial volunteer cannot attend a trial site, then delivery of IMP to a patient's home is acceptable and no substantial amendment notification to PPB will be required.

Sponsors should do a risk-assessment and record this internally.

Participants must consent verbally (and this should be documented in their notes) to providing contact details for shipping purposes. If the participant does not want to sign for the delivery due to self-isolation, then a follow up phone call could be used to confirm they have received the package. The sponsor should also consider if any training is required for administration of the IMP.

The following factors need to be taken into consideration if providing an IMP to a participant at home:

Storage requirements:

- Whether the medicine has any specific storage requirements, and how those are managed during posting
- What assurance can be given about the integrity of the product during transit, for example should a temperature monitoring device be used

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- The stability of the product and margin of safety: for example a product with a very stable profile at temperature extremes would require less monitoring than one with a narrow stability range. The expiry of the product may need to be shortened if is delivered in ambient temperature

Medicine accountability

- The mechanism for confirming that the subjects have received the IMP, and it has not been delivered to someone else
- Whether the medicine needs to be signed for and sent by courier or recorded delivery
- Whether there needs to be a follow-up call to the subject
- Adherence to taking medication should be emphasised. Reminder through phone calls or any other methods, is encouraged to ensure adherence and ensure that participant are taking the right dose and at the right time.

Replacing in-person visits with phone calls

Using phone calls instead of protocol-directed in-person study visits is acceptable where possible. This will not constitute a serious breach of the protocol. A substantial amendment to update the protocol will not be required. We would however expect that any protocol deviations are well documented. However, this needs to be agreed upon between the study site and the sponsor.

‘Dear Investigator’ Letters

During the COVID -19 pandemic it is acknowledged that Sponsors may need to send ‘Dear Investigator’ Letters to inform investigator sites of changes to trial conduct. These do not require regulatory oversight and should not be submitted to the PPB.

Reporting of serious adverse events (SAEs), and submission of annual safety reports (DSURs) and end of trial notifications

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We appreciate that capacity issues related to COVID-19 may prevent timely reporting. If this occurs, report this as soon as possible after the capacity issue is resolved. All safety reports should preferably be submitted as the required guidelines and submissions should be done through the online portal.

Deviation from protocol defined timelines in this case does not require a substantial amendment to PPB.

Particular attention should be paid to timely reporting of suspected unexpected serious adverse reactions (SUSARs) which put participant safety at risk on a trial or have the potential to impact participants of other trials.

These should in addition be reported through the online portal (www.ctr.pharmacyboardkenya.org)

Protocol deviations and serious breaches

Patients may be advised to stay away from clinical trial sites due to existing health problems that may put them at risk of infection, or they may be reluctant to travel to sites where there are high densities of people.

They may also have been advised to self-isolate as a precaution or as a result of confirmed infection so are unable to undertake required clinical trial activities.

There will therefore be an increase in protocol deviations. Please ensure they are well documented, to enable appropriate evaluation for the trial. These should in addition be reported through the online portal (www.ctr.pharmacyboardkenya.org)

Protocol deviations should be reported to PPB in the usual manner or collected and submitted in bulk form at the end of the crisis.

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Protocol waivers

Prospective protocol waivers remain unacceptable. We would not expect you to bypass the eligibility process due to difficulties in assessing subjects and carrying out tests.

Safety of patients remains a priority and they should not be included into a trial unless you can confirm they meet the inclusion and exclusion criteria.

Similarly, if the safety of a trial subject is at risk because they cannot complete key evaluations or adhere to critical mitigation steps, then consideration to discontinuing that subject must be discussed.

This may also extend to the whole trial in some cases, and a Sponsor and Investigator should remember they can use Urgent Safety Measures, or even temporarily halt a trial, or halt recruitment, if this is the best way forward.

Subject safety

Subject safety is of the highest priority. Sponsors should consider the risk/benefit of conducting trials in medicines that act as immunosuppressants, for example in early phase healthy volunteer trials, where there is no therapeutic benefit to the volunteer, but taking part in the trials does pose a risk of infection.

Signatures

If your processes require wet-ink signatures, consider alternative methods of demonstrating approvals, such as email confirmation.

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New studies relating to COVID-19

The Pharmacy and Poisons Board has made available an expedited review process (with a target of ten working days) for studies relating to COVID-19 where there are public health grounds for rapid review. The expedited review will include among others

1. Joint review with the ethics review committees and other regulators
2. Parallel submission to ethics review committees and other regulators
3. Availability of a pre-submission meeting (through video or teleconferencing) with sponsors and investigators to clarify on issues before formal submission of a clinical trial application (request for a meeting at www.ctr.pharmacyboardkenya.org)
4. Being part of the WHO AVAREF submission and review for clinical trials to be carried out in multiple African countries

Help from the PPB

The clinical trials unit of the Pharmacy and Poisons Board is available to respond to any queries or clarifications through

email; cta@pharmacyboardkenya.org and [Tel: +254 709 770 100](tel:+254709770100)

The Pharmacy and Poisons Board encourages investigators and sponsors to seek guidance anytime during this period concerning ongoing and proposed clinical trials for optimal coherence in the conducting clinical trials during the period of COVID-19 pandemic. Safety of study participants remains the top priority.

COVID-19 and the challenges of responding to it are rapidly evolving and this guidance will be updated in response to changes globally and in Kenya, and to reflect feedback received from you and our other stakeholders in the clinical trial

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