GUIDELINES ON THE REVIEW AND CONSIDERATION OF APPLICATIONS FOR MONITORED EMERGENCY USE OF UNREGISTERED AND EXPERIMENTAL INTERVENTIONS AND OFF-LABEL PRODUCTS USE IN UGANDA

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Adoption and approval of these professional guidelines

In EXERCISE of the powers conferred upon the Drug Authority by Section 5(i) of the National Drug Policy and Authority Act, Cap. 206 of the Laws of Uganda (2000 Edition), the Drug Authority hereby ADOPTS and ISSUES these Professional **"Professional Guidelines on the Review and Consideration of Applications for Monitored Emergency Use of Unregistered and Experimental Interventions and Off-Label Products Use in Uganda"**

Doc. No. DPS/GDL/045, Revision No.: 0", made this 15th day of February 2023, that take effect on 20th February 2023.

Signature _____

Dr. Medard Bitekyerezo

CHAIRPERSON

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Kampala, Uganda

1.0 BACKGROUND

Clinical trials are the gold standard for generating evidence for the safety and efficacy of interventional products. However, in the context of diseases of public health importance for which no proven intervention exists and for which an outbreak that is characterized by high mortality occurs, the World Health Organization (WHO) recommended that it may be ethically appropriate to offer individual patients investigational interventions on an emergency basis ***outside of clinical trials*** [1]. Monitored Emergency Use of Unregistered Investigational Interventional Products (MEURI) is an ethical framework that was adopted by the WHO Ethics Working Group as a mechanism of testing unproven biomedical interventions including vaccines as potential treatments in the context of public health emergencies with the following conditions:

a) Informed consent is obtained;

b) The principles of Good Clinical Practice are followed; and

c) Other local applicable regulatory requirements are met.

The WHO recommends that local regulatory requirements are met and, given the nature of the disease/epidemic, every effort should be made to document safety events and where possible efficacy.

This Guideline is intended to domesticate the above framework in the context of the already existing legal and regulatory framework in Uganda.

1.1 RATIONALE

The WHO developed an ethical framework known as Monitored Emergency Use of Unregistered Interventions (MEURI), which established the following criteria to be met for access to investigational therapeutics for individual patients outside of clinical trials[1]. The framework is intended for conditions where there is no proven treatment and there are drugs under development that have demonstrated efficacy and safety in laboratory and animal models. On a strictly exceptional basis it may be ethically and scientifically permissible to use an unproven intervention outside clinical trials for the clinical benefit of individual people or groups or to benefit populations if the monitored emergency use meets the rigorous ethical criteria spelled out by the MEURI ethical framework.

The WHO expert panel recommended that access to and use of investigational therapeutics under MEURI be carefully considered for each individual patient, including for vulnerable populations such as pregnant women and pediatric patients/populations at risk, as appropriate given the available data. In general, the expert panel recommends that factors including disease severity, available information on risks and

benefits for the investigational therapy (including any available information on adverse effects in pregnancy or pediatrics) be considered.

1.2 OBJECTIVE

1.2.1 This guideline provides a framework for the review of applications to National Drug Authority (NDA) for approval of protocols under the WHO framework of **Monitored Emergency Use of Unregistered Investigational Interventional Products (MEURI),** in the context of public health emergencies, declared by the Ministry of Health to enable the at-risk populations of Uganda to have access to drugs at all times.

1.2.2 This guideline will be implementable in line with Section 8(4) of the National Drug Policy and Authority Act Cap 206 that gives NDA the mandate to facilitate access of emergency medicines not listed on the National formulary.

1.2.3 Components of this guideline have been adopted from the WHO Guidance for Managing Ethical Issues in Infectious Disease Outbreaks.[2]

1.2.4 Ethical basis for MEURI is justified by the ethical principle of respect for patient autonomy — i.e. the right of individuals to make their own risk–benefit assessments in light of their personal values, goals and health conditions. It is also supported by the principle of beneficence — providing patients with available and reasonable opportunities to improve their condition, including measures that can plausibly mitigate extreme suffering and enhance survival.

1.2.5 Scientific basis for MEURI: This committee should base its recommendations on a rigorous review of all data available from laboratory, animal and human studies of the intervention to assess the risk–benefit of MEURI in the context of the risks for patients who do not receive the Investigational Product.

1.3 SCOPE

This guideline applies to the review of applications and approval of use of unregistered investigational products including off-label product use, for prophylaxis or treatment of individuals in situations of outbreaks characterized by high mortality for pathogens where no proven treatment exists. The MEURI ethical framework does not include unproven diagnostic devices or products, and its application to them may require special ethical and regulatory considerations.

1.4 POLICY

Section 8(4) of the National Drug Policy and Authority Act CAP 206 states that (4) Notwithstanding subsection (3), a drug not appearing on the national formulary may

be imported and sold after authorisation by the drug authority to meet emergency or extraordinary circumstances.

1.5 RESPONSIBLITY

1.5.1 The Ministry of Health (MoH)

The Ministry of Health holds the overall responsibility for health of the Ugandan population. The Ministry of Health has the mandate to provide the highest possible level of health services to all people in Uganda through delivery of promotive, preventive, curative, palliative and rehabilitative health services at all levels.

The MoH will release timely notifications of any outbreak and will convene the Scientific Advisory Committee to discuss and recommend the mechanisms that will be followed during each outbreak.

The MoH will also establish structures that will monitor and report on Safety of Interventional Products during outbreaks.

1.5.2 National Drug Authority (NDA)

The National Drug Authority is responsible for provision of technical support in the review of the scientific protocol, investigators brochure and other relevant documentation to guide the use of the investigational product/off-label product in line with the MEURI framework.

NDA will also authorize the importation of the unregistered investigational interventional products or off-label products in line with the provisions of the National Drug Policy and Authority Act, CAP 206, the National Drug Policy and Authority (Importation and Exportation of Drugs) Regulations 2014 and the Guidelines for verification of applications for importation of drugs for emergency or extraordinary circumstances.

The National Drug Authority, through the existing frameworks will facilitate targeted safety monitoring of the deployed products.

NDA will advise on the discontinuation of approved interventions under the MEURI framework based on the growing scientific evidence on efficacy and safety of the product. If emerging scientific (safety and efficacy) data casts doubt on the continued benefit of the investigational medicinal products, NDA will recommend discontinuation of the use of these products. This decision will be based on information from use within the country or from the international scientific community.

1.5.3 Uganda National Council for Science and Technology (UNCST)

The Uganda National Council for Science and Technology is responsible for providing effective and innovative leadership in the development, promotion and application of Science and Technology and its integration in the response to the emergency situation or disease outbreak in line with the applicable ethical considerations to ensure that safety of all is prioritized.

The UNCST will guide on the Research Ethics review process for justification of MEURI during outbreaks. The UNCST as the secretariat for the conduct of joint scientific and ethical reviews will convene a Joint Scientific and Ethical review for consideration of the Investigational or off label product.

1.5.4 Uganda National Health Research Organization (UNHRO)

Uganda National Health Research Organization shall provide stewardship of research agenda; ensuring good practices and ethics in the conduct of health research to warrant that the lessons learned from dealing with one outbreak are transferrable to another.

UNHRO will contribute to the regulatory review process and shall provide guidance in line with the national health research plan, provide clearance for publications and make periodic assessments of the research institutes.

2.0 CRITERIA FOR APPLICATION

Based on the criteria developed by the WHO for access to investigational therapeutics for individual patients outside clinical trials, the review and consideration of applications for use of unregistered investigational interventional products including off-label product use under the MEURI framework will be in response to emergency or extraordinary circumstances. This should hinge on the principles similar to those that govern the use of investigational products for clinical trials described here below:

a) Importance of ethical and regulatory oversight: - MEURI is intended to be an exceptional measure for situations in which initiating a clinical trial is not feasible, not as a means to circumvent ethical oversight of the use of unproven interventions;

b) Effective resource allocation: - MEURI should not delay the initiation of clinical research into experimental products or resources from the implementation of effective clinical care and/or public health measures that may be crucial to control an outbreak;

c) Minimizing risk: - Administering unproven interventions necessarily involves risks, some of which will not be fully understood until further testing is conducted.

Only investigational products manufactured according to good manufacturing practices should be used for MEURI.

d) Collection and sharing of meaningful data: - Physicians overseeing MEURI have the same moral obligation to collect all scientifically relevant data on the safety and efficacy of the intervention as researchers overseeing a clinical trial.

e) Importance of informed consent: - Individuals who are offered MEURI should be made aware that the intervention might not benefit them and might even harm them. The process of obtaining informed consent to MEURI should be carried out in a culturally and linguistically sensitive manner, with an emphasis on the content and understandability of the information conveyed and the voluntariness of the patient's decision

f) Need for community engagement: - MEURI must be sensitive to local norms and practices. One way to try to ensure such sensitivity is to use rapid "community engagement teams" to promote dialogue about the potential benefits and risks of receiving

g) Fair distribution in the face of scarcity: - Compounds qualifying for MEURI may not be available in large quantities. In this situation, choices will have to be made about who receives each intervention.

The criteria for the authorization of MEURI applications is based on;

a) Notification of a public health emergency or potential threat by the Ministry of Health;

b) The nature of disease for which the investigational medicine is to be taken should be either fatal, life threatening or severely debilitating as defined below;

   i. Fatal; possibility of causing death to the victim.

   ii. Life-threatening means diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival. The criteria for life-threatening do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before review at a convened meeting of the Institutional Review Board (IRB) is feasible.

   iii. Severely debilitating means diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of an arm, leg, hand or foot, loss of hearing, paralysis or stroke.

c) Evidence that there is no proven effective treatment for the disease or that proven effective interventions are not part of national policy;

d) Immediate initiation of clinical trials is not possible.

e) Data that provides preliminary support of the intervention's efficacy and safety are available, at least from laboratory or animal studies, and use of the intervention outside clinical trials has been suggested by an appropriately qualified scientific advisory committee on the basis of a favorable risk-benefit analysis.

f) Approval of such use had been granted by a Research Ethics Committee (REC) and cleared by the Uganda National Council for Science and Technology.

g) Approval of use has been granted by the Ministry of Health to meet a public Health need.

h) A comprehensive pharmacovigilance and risk management plan have been developed by the manufacturer of the drug depending on the risk profile of the medicine to be used under guidance from the National Drug Authority.

i) Appropriate Informed consent from the patient is obtained.

j) There is an appropriately trained monitoring or safety committee to monitor the emergency use of the intervention.

k) Results are adequately documented according to the principles of Good Clinical Practice and shared in a timely manner with the local and other relevant authorities.

l) The following documents should be in place prior to the emergency use of the intervention and where applicable these documents should be in compliance with the principles of Good Clinical Practice:

   i. A signed protocol that clearly indicates the responsible physician(s) and person responsible for the investigational interventions

   ii. An up-to-date Investigator's Brochure or other reference safety document.

   iii. Evidence for the quality and source of the investigational intervention including the Certificates of Analysis, certificate of Good Manufacturing Practice (GMP) for the manufacturing facility.

   iv. Laboratory confirmation of the disease by an authorized and accredited laboratory.

   v. Standard Operating Procedures for:

1. Handling the interventional drugs and any ancillary medicines: supply/receipt, storage, dispensing, accountability and disposal.
2. Treatment decisions such as interruption or discontinuation due to adverse events, patient non-compliance, etc
3. Obtaining informed consent in an emergency situation.

vi. Where a vaccine is the interventional product, the engagement plan for the Adverse Events Following Immunisation (AEFI) committee will be submitted.

3.0 REGULATORY REVIEW AND OUTCOME

Given the current legal and regulatory framework, National Drug Authority may only authorize drug-related clinical trials. Based on the premises that the use of unregistered investigational products during public health emergencies is done *outside the context of clinical trials*, the Minister of Health will delegate the responsibility of the regulatory approval of the Investigational Medicinal Product to the National Drug Authority. Thereafter, in consultation with technical experts who will constitute a National Task Force, will consider and approve the deployment plan following NDA approval of the unregistered investigational products or repurposed registered products (off-label) for use in the outbreak. The review of protocols for therapeutic use of the investigational products will be done jointly by a taskforce constituting a representative(s) from the following institutions and/or disciplines:

a) Ministry of Health;
b) National Drug Authority (with representation from the Directorate of Product Safety and Directorate of Inspection and Enforcement);
c) Uganda National Council for Science and Technology;
d) Uganda National Health Research Organization;
e) The Forum for Research Ethics Committee Chairpersons of Uganda (FRECU);
f) A technical expert(s) in the therapeutic area of interest such as immunologist, vaccinologist, microbiologist, Infectious Diseases Specialist; and
g) A community representative.

National Drug Authority will give a letter of no objection (Appendix 1) on the use of the proposed unregistered intervention based on the outcome of the joint ethical and scientific review and internal review of all the information submitted.

The National Drug Authority will authorize the importation of the unregistered investigational interventional products-including off-label products, in line with the

provisions of the National Drug Policy and Authority (Importation and Exportation of Drugs) Regulations 2014 and the Guidelines for verification of applications for importation of drugs for emergency or extraordinary circumstances.

National Drug Authority will follow up Adverse Drug Reactions (ADRs) in line with the National Drug Policy and Authority (Pharmacovigilance), Regulations 2014 and the National Drug Policy and Authority (Pharmacovigilance) (Amendment) Regulations 2021.

National Drug Authority shall reserve the right to perform due diligence and grant or decline importation requests under section 8(4) in consideration of safety, efficacy and quality; and in consideration of new information about drug products that may arise from time to time.

3.1 Expectations for researchers conducting research under the MEURI framework;

3.1.1 The Ministry of Health shall take the lead on the implementation of use of medications under the MEURI framework and as such, all researchers intending to use products under this framework will collaborate with the Ministry of Health.

3.1.2 The Principles of Good Clinical Practice will apply to the implementation of the MEURI framework due to the use of investigational products for which there is limited data to guide the use.

3.1.2 Investigational products shall be manufactured according to current Good Manufacturing Practice and meet the labelling requirements for investigational products as prescribed in the National Drug Policy and Authority (Conduct of Clinical Trials) Regulations.

3.1.3 Given the potential risk of harm from the Investigational medicinal product, informed consent will be sought. Public health practitioners should also be aware of the measures that should be taken to protect both privacy and confidentiality during emergency response.

3.1.4 Records should be easily accessible and retrievable for accurate reporting, verification and interpretation.

3.1.5 When new scientific knowledge is generated to protect the public during an emergency, relevant findings shall be publicized in due time. However, such knowledge will be subject to further evidence generated through clinical trials to inform market authorization of the products.

4.0 REFERENCES

Emergency use of unproven clinical interventions outside clinical trials: ethical considerations: 2022. World Health Organization.

National Drug Policy and Authority (Conduct of Clinical Trials) Regulations 2014

National Drug Policy and Authority Act, Cap 206

World Health Organization, 2016, Guidance For Managing Ethical Issues In Infectious Disease Outbreaks, https://apps.who.int/iris/bitstream/handle/10665/250580/9789241549837-eng.pdf;jsessionid=9961C677EA1F0C720E8D02A19BE9947B?sequence=1

World Health Organization, 2018, Notes for the record: Consultation on Monitored Emergency Use of Unregistered and Investigational Interventions(MEURI) for Ebola Virus Disease (EVD). https://www.who.int/ebola/drc-2018/notes-for-the-record-meuri-ebola.pdf

APPENDIX 1

Letter of No objection to the proposed MEURI protocol Implementation

(Date)

(Address)

Dear Sir,

RE: Study title

In line with the proposed MEURI framework and the recommendations of…. (Expert group that made the recommendation)…on regarding the use of unregistered investigational products for the treatment and/or prophylaxis of… (disease) …..the NDA hereby provides a final response

Based on the review, the following issues and recommendations have been noted for your information which if addressed, would further improve the quality of the protocol and its scientific value:

1.
2.

Please be advised as follows;

1. Regulation 3(1) of the NDP&A (Pharmacovigilance regulations 2014) require establishment of an appropriate system for pharmacovigilance to manage the safety data for drugs for human use.
2. Regulation 3(1) mandate the Authority to request submission of reports that may be relevant to determine the safety, efficacy and quality of the drugs.

National Drug Authority wishes you the best in the implementation of this protocol.

Yours sincerely,

Secretary to the Authority

DOCUMENT REVISION HISTORY

Date of revision	Revision number	Document Number	Author(s)	Changes made and reasons for revision
15 Feb 2023	0	DPS/GDL/045	*Authors:* 1. Dr Rachael Kyeyune Bakyayita 2. Sheila Ampaire *Reviewers* 1. Sharon Kiggundu 2. Dr Ian Mugisa 3. Florence Wanyenze 4. Pius Ariho Mugumya 5. Ntale Ismail 6. Dr. Helen Byomire Ndagije	Document First Issue

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