Republic of the Philippines
Department of Health
OFFICE OF THE SECRETARY

ADMINISTRATIVE ORDER
No. 2021 - _____

SUBJECT: Guidelines on the Sponsorship of DOH in the Conduct of Clinical Trials for COVID-19 Investigational Products

I. RATIONALE

The COVID-19 pandemic has disrupted the daily lives of the people worldwide. The SARS-CoV-2 virus, which originated in China, continuously spreads around the globe, causing countries to come up with measures in preventing the fast transmission of the virus that eventually develops into COVID-19 disease. On March 11, 2020, the World Health Organization (WHO) declared COVID-19 as a pandemic with more than 118,000 cases in 114 countries and 4,291 deaths.

The first COVID-19 case in the Philippines was reported in January 2020. As of June 29, 2021, there are over 1,390,000 cases and more than 24,300 recorded deaths in the Philippines. Safety and health measures are strictly observed such as imposed city-wide lockdowns, mass quarantines, and observance of proper hygiene and social distancing in order to help mitigate the spread of the disease in the country.

The Department of Health (DOH) is actively responding to the prevention, monitoring, and implementation of treatment guidelines for COVID-19, in coordination with the Inter-Agency Task Force (IATF) for the Management of Emerging Infectious Diseases, other government agencies, medical societies, and the local government units. Moreover, it has been participating as a sponsor in the WHO Solidarity Trial for therapeutics and as co-lead for the Solidarity Trial for vaccines. It is in this light that a guideline for the conduct of DOH-sponsored clinical trials is critical in order to protect the welfare of the patients being treated with investigational products for COVID-19. Hence, the DOH is adopting the IATF guidelines for the conduct of clinical trials as well as the provisions of the Administrative Order (AO) No. 2020-0010 on the regulations on the conduct of clinical trials for investigational products.

II. OBJECTIVES

A. General Objective

This Order aims to establish standard guidelines and procedures on the sponsorship of clinical trials for COVID-19 investigational products by the DOH.

B. Specific Objectives

1. To adopt the current guidelines of the Food and Drug Administration (FDA) Philippines and international guidelines in the sponsorship of clinical trials for COVID-19, which will be sponsored by the DOH.
2. To identify the roles, responsibilities, and accountabilities of concerned internal and external stakeholders in clinical trials for COVID-19 investigational products sponsored by the DOH.

III. SCOPE OF APPLICATION

This Order shall apply to all DOH units and offices, Ministry of Health – Bangsamoro Autonomous Region in Muslim Mindanao (BARMM) as provided for in RA No. 11054 Organic Law for the BARMM, Local Government Units (LGUs), contract research organizations (CROs), research institutions, investigators, research ethics committees (RECs) and other stakeholders involved in the conduct of clinical trials for COVID-19 investigational products sponsored by the DOH.

IV. DEFINITION OF TERMS

A. **Adverse Drug Reaction (ADR)** refers to all noxious and unintended responses to a medicinal product related to any dose (International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) E2A - Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

B. **Adverse Event (AE)** refers to any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment (ICH E2A).

C. **Clinical Trial/Study** refers to any investigation in human subjects intended to discover or verify the clinical, pharmacological, and/or other pharmacodynamic effects of an investigational product(s), and/or identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy (ICH GCP 1.12)

D. **Contract Research Organization (CRO)** refers to a service organization that provides support to the pharmaceutical and biotechnology industries in the form of outsourced pharmaceutical research services (for both drugs and medical devices).[i]

E. **Data Safety Monitoring Committee (DSMC)** refers to an independent group of experts that advises the DOH as the sponsor of clinical trials (DSMC Standard

Operating Procedures (SOP)).

F. **DOH Steering Committee (SC)** refers to a body created to ensure the necessary oversight in the administration of the investigational therapies for COVID-19 patients and ensure their safety and well-being (DPO No. 2020-1377).

G. **Good Clinical Practice (GCP)** refers to an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects.[ii]

H. **International Conference on Harmonization of Good Clinical Practice (ICH-GCP)** refers to a harmonized standard that protects the rights, safety, and welfare of human subjects, minimizes human exposure to investigational products, improves the quality of data, speeds up marketing of new drugs and decreases the cost to sponsors and the public.[iii]

I. **Institutional Review Board (IRB)/Institutional Research Ethics Committee (REC)/Institutional Ethics Review Board (IERB)/Research Ethics Review Committee (ERC)** refers to an independent body constituted of medical, scientific, and non-scientific members, whose responsibilities are to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing a continuing evaluation of trials, protocols and amendments, and of methods and materials to be used in obtaining and documenting informed consent of the trial subjects (ICH GCP 1.31).

J. **Investigational Product (IP)** refers to a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH GCP 1.33).

K. **Principal Investigator (PI)** refers to the responsible leader of a team of individuals in a trial site (E6 (R2) 1.34).

L. **Single Joint Research Ethics Board (SJREB)** refers to a duly accredited research ethics committee organized by the Department of Health that facilitates the review of multi-site health research protocols in the country. It is also the REC that has oversight for DOH-sponsored/funded protocols.

M. **Sponsor** refers to an individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a clinical trial (ICH GCP 1.53).

N. **Suspected, Unexpected, Serious Adverse Reaction (SUSAR)** refers to a serious adverse reaction, the nature, severity, or outcome of which is not consistent with the reference safety information (e.g., investigator's brochure for investigational product or summary of product characteristics for an authorized product) (AO No. 2020-0010).

V. GENERAL GUIDELINES

A. All clinical trials for COVID-19 investigational products (IPs) that will be sponsored by the DOH shall comply with the most recent research and ethics guidelines set forth by the local and international guidelines such as but not limited to the National Ethical Guidelines by the Philippine Health Research Ethics Board (PHREB), ICH-GCP, Council for International Organizations for Medical Science (CIOMS) and Declaration of Helsinki.

B. All DOH-sponsored clinical trials for COVID-19 IPs shall abide by the requirements set forth by the local regulatory bodies such as the Philippine FDA and the PHREB, and the guidelines provided by the Inter-Agency Task Force (IATF) for the Management of Emerging Infectious Diseases, as may be applicable. The basic requirements for application of ethical clearance by the SJREB are provided in Annex A. These shall be submitted by the principal investigator (PI) or proponent to the said agency/committee for review and approval.

C. All parties involved in the conduct of clinical trials for IPs, including DOH units and offices, investigators and site staff, and CRO, among others shall abide by the ICH-GCP guidelines and current National Ethical Guidelines for Health and Health-Related Research of the Philippine Health Research Ethics Board (PHREB) as they perform their duties and functions and shall undergo clinical research-related training and capacity-building activities, e.g., GCP training.

D. Sponsorship by the DOH of IPs shall not be construed as an automatic endorsement of the use of the IP and/or its manufacturer, nor of guaranteed purchase by the DOH or PhilHealth. Recommendations related to the use or purchase/payment of such IPs shall be subject to existing policies related to practice guideline development, health technology assessment, and benefit package development. In addition, sponsorship by the DOH of IPs shall not be construed as a commitment to sponsor Phase IV clinical trials of these IPs - these shall be borne by the companies/manufacturers that have obtained FDA registration for these products.

E. DOH shall preferentially sponsor trials on a co-sponsorship basis with equal sharing of risk exposures, and reserves the exclusive right to delegate sponsorship obligations, as it deems appropriate, to co-sponsors, implementing institutions, trial investigators, and third-party research organizations (should these be tapped). Delegation of such obligations shall not be open to negotiation, and must be complied with by co-sponsors, implementing institutions, trial investigators, and third-party research organizations.

F. Any processing and/or disclosure of sensitive personal information or personal information shall comply with the provisions of the Republic Act No. 10173 or the "Data Privacy Act," its Implementing Rules and Regulations and the relevant issuances of the National Privacy Commission.

VI. SPECIFIC GUIDELINES

A. Process of Application for DOH Sponsorship

1. The clinical trial protocol for COVID-19 IPs to be considered for DOH sponsorship shall be submitted by the proponent to the SC secretariat for general assessment based on the following key criteria:
    a. part of WHO or any multilateral and bilateral agreements, efforts, and initiative;
    b. identified as national government priority thru explicit documentation (e.g., IATF resolutions, Presidential Management Staff (PMS) directives, high-level government agreements, DOH research agenda, and/or emerging local and international scientific evidences);
    c. with some evidence of potential clinical benefit;
    d. clear terms of agreement regarding IP ownership and insurance coverage such as study insurance and product liability insurance;
    e. availability of data safety monitoring committee; and,
    f. available funding to cover costs of both the conduct and management of the clinical trial in accordance with ICH-GCP.

2. All proposals for COVID-19 clinical trials for possible DOH sponsorship shall be coursed through the DOH Steering Committee for the Conduct of Clinical Trials for COVID-19 Investigational Treatment (SC) for review and recommendations.

3. COVID-19 clinical trial proposals shall undergo the usual technical evaluation by the Department of Science and Technology - Philippine Council for Health Research and Development (DOST- PCHRD) which shall provide technical oversight of the conduct of clinical trials.

4. For studies seeking sponsorship from the DOH, the monitoring body responsible for assessing results and formulating recommendations to the DOH SC shall be the DOH Data Safety Monitoring Committee (DSMC). While for studies seeking co-sponsorship with DOH, it is recommended that these shall have an identified DSMC. Likewise, proponents seeking sponsorship or co-sponsorship are advised to provide recommended experts that can act as temporary members to the DOH DSMC, should the need arise. Nominated experts shall be assessed for the necessary qualifications and experience and final selection shall be determined by the SC. Pursuant to the provisions of Department Order No. 2017-0332 (*Guidelines on the Disclosure and Management of Conflict of Interest in Relation to the Use of Pharmaceutical Products and Medical Devices*), temporary members of the DSMC shall disclose any potential Conflict of Interest (COI) and sign a Non-Disclosure Agreement or Confidentiality Agreement and/or execute a Data Sharing Agreement, if applicable, to ensure that confidential and personal information, if any, shall be protected under this undertaking.

5. The secretariat shall inform the SC of the result of the preliminary assessment and screening of the applications for correctness and completeness, for their information, further assessment, and recommendation. If the submission passed the key criteria, as concurred by the SC, this shall be forwarded to the DOST for further technical evaluation. Otherwise, the SC secretariat shall communicate the deficiencies in the application to the trial proponents.

6. The minimum acceptable profiles of the candidate IPs include the following:
    a. Adverse event profile supports advancement to Phase IIb/III clinical trials;
    b. Data from animal and human studies support an acceptable efficacy and safety profile;
    c. Stability of data is sufficient to assure delivery of dose to be tested;
    d. Manageable regimen considering resource settings; and,
    e. Demonstrated capability to rapidly scale up production to allow inclusion in broader trial use.

7. Annex C details the decision algorithm that will guide the recommendation making of the Steering Committee whether to approve or disapprove the proposal for DOH sponsorship.

B. Trial Management

1. In the interim, implementing institutions partnering with DOH on the sponsorship and conduct of clinical trials for COVID-19 shall be responsible for trial management, quality assurance, safety monitoring and reporting, and other obligations as may be necessary. The parties shall coordinate with each other and decide as to how the parties will go about to facilitate the transition once the office under the University of the Philippines-National Institute of Health ("UP-NIH") is established.

2. Once the *National Clinical Research Center (NCRC) or the Clinical Trial Research Center under the University of the Philippines- National Institutes of Health (UP-NIH)* has been established, it shall manage all DOH sponsored COVID-19 clinical trials.

3. In instances when supplemental funding is available, fund transfer of internally pooled research funding of DOH to be administered by the DOST-PCHRD shall be facilitated by HPDPB-HRD in line with its existing rules, policies, and timelines. Otherwise, fund transfers shall be facilitated by the primary funding DOH unit. A Certificate of Availability of Funds (CAF) must be secured by the proper party and prescribed auditing and accounting rules must be strictly complied with.

4. The Clinical Trial Research Center and the CRO shall follow the guidelines

stipulated in the DOH AO No. 2020-0010 with the subject, *"Regulations on the Conduct of Clinical Trials for Investigational Products."* This is accessible through the FDA website at https://www.fda.gov.ph/?s=clinical+trial.

5. For clinical trials for investigational COVID-19 vaccines, the Clinical Trial Research Center and the CRO shall additionally comply with Resolution No. 65 s. 2020 Section C of the IATF for the Management of Emerging Infectious Disease which specifies the recommendations of the Sub-Technical Working Group on Vaccine Development. Further guidance is provided in FDA Circular No. 2020-029, entitled, "Guidance on Applications for the Conduct of COVID-19 Clinical Trials."

C. DOH Steering Committee for COVID-19 Clinical Trials for Investigational Treatments

1. The Steering Committee (SC) was established through DPO No. 2020-1377 and reconstituted through DPO No. 2021-0923 dated 19 April 2021. The SC is composed of the following DOH offices and other relevant stakeholders:

a. Chair: Health Regulation Team
b. Vice-chair: Public Health Services Team
c. Members:

i. Disease Prevention and Control Bureau (DPCB)
ii. Health Policy Development and Planning Bureau (HPDPB)
iii. Bureau of International Health Cooperation (BIHC)
iv. Department of Science and Technology – Philippine Council for Health Research and Development (DOST-PCHRD)
v. Pharmaceutical Division (Secretariat)

D. DOH Data Safety Monitoring Committee (DSMC)

1. The SC established the DOH DSMC through DPO No. 2020-300, entitled, "*Creation of the Data Safety Monitoring Committee to Provide Guidance to the Department of Health Steering Committee for the Conduct of Clinical Trials for Investigational Treatment for COVID-19*", which is composed of at least three (3) or more members depending on the nature and representation requirement of the trial to be conducted. The composition of the DSMC is as follows:

a. Chair
b. Members:

i. Subject matter expert
ii. Biostatiscian
iii. Clinical Trialist

VII. Roles and Responsibilities

A. The Secretary of Health shall appoint the members of the Steering Committee and DSMC.

B. The Bureau of International Health Cooperation (BIHC) shall:

1. Coordinate with concerned offices/agencies for the donated foreign IPs;
2. Provide assistance in securing of import clearance for donated IPs; and,
3. Assist in sourcing of funds from international partners.

C. The DOH Data Safety Monitoring Committee (DSMC)* shall:
   1. Conduct safety monitoring and review;
   2. Formulate recommendations to the DOH SC on trials for consideration and appropriate actions; and,
   3. Review the following:
      a. Interim/cumulative data for evidence of study-related adverse events, efficacy, data quality, completeness and timeliness
      b. Performance of individual centers (for multi-site studies)
      c. Adequacy of compliance with goals for recruitment and retention
      d. Adherence to protocol
      e. Factors that might affect the study outcome or compromise the confidentiality of the trial data
      f. Factors external to the study (i.e., scientific or therapeutic developments) that may impact participant safety or the ethics of the study.

   **Once the UP NCRC is established, these responsibilities shall be taken over by the DSMC that will be created under the UP NCRC.*

D. The Food and Drug Administration (FDA) shall:
   1. Process clinical trial related applications such as Clinical Trial Approval and Amendments and Import License (IL) for the COVID-19 IPs in accordance with the Administrative Order No. 2020-0010; as well as License to Operate (LTO) for entities that intend to conduct COVID-19 clinical trials in accordance with the Administrative Order No. 2020-0017.

   2. Conduct inspections in facilities of investigational sites, sponsors, CROs and RECs engaged in the conduct of clinical trials to ensure that the rights, safety, and well-being of study subjects have been protected, to ensure integrity of the scientific data collected, and to assess adherence to GCP Principles and other applicable FDA regulations.

E. The Health Policy Development and Planning Bureau – Health Research Division (HPDPB-HRD) shall:
   1. Provide secretariat support to the DOH DSMC;
   2. Arrange and coordinate the conduct of GCP trainings for the DOH; and,
   3. Provide technical assistance to facilitate the procurement process and/or transfer of funds that will be used for the sponsorship of COVID-19 clinical trials to the DOST-PCHRD.

F. The Disease Prevention and Control Bureau (DPCB) shall:
   1. Provide additional technical and funding support for the implementation of DOH-

sponsored COVID-19 clinical trials, including budget support for trial management and/or procurement of investigational drugs as necessary.

2. Undertake negotiated procurement to transfer funds to third parties and/or facilitate supplemental procurement of investigational drugs as deemed necessary.

G. The Pharmaceutical Division (PD) shall:

1. Provide secretariat support to the DOH SC;
2. Initially assess the completeness of the documentary requirements submitted by external proponents/institutions; and,
3. Document the proceeding of SC meetings and maintain all pertinent records and minutes of the meetings.

H. The DOH Steering Committee (SC) shall:

1. Provide oversight functions in the conduct of DOH-sponsored clinical trials for investigational therapies and vaccines for COVID-19;
2. Develop strategic plans, policy guidelines and mechanisms for the conduct of clinical trials for investigational treatment for COVID-19 infection in participating hospitals;
3. Provide strategic advice to enhance the performance and efficiency of clinical trial operations and timelines, such as collaboration among DOH offices and other relevant parties involved;
4. Ensure that clinical trial investigators and participating hospitals are following the approved protocols of SJREB and the FDA;
5. Review and decide on requests for DOH sponsorship of clinical trials that are judged to be scientifically sound and clinically important; and,
6. Decide on reported issues and other technical and administrative concern arising from the trials.

I. CRO/ UP NIH- Clinical Trial Research Center shall:

1. Facilitate the clinical trial application to the FDA;
2. Manage the conduct of all the DOH - sponsored clinical trials;
3. Ensure that the clinical trial protocol is followed;
4. Create its own DSMC; and,
5. Provide all the necessary reports requested by the DOH and DOST.

VIII. Allocation of Funds

1. A pool of funds for the conduct of DOH-sponsored clinical trials for COVID-19 shall be created and will be lodged to the DOH – HPDPB-HRD. Moreover, funding shall be coordinated with the DOH – Administration and Financial Management Team.
2. The BIHC shall actively seek counterpart funding from international health partners (IHPs) for the conduct of the DOH-sponsored clinical trials for COVID-19 IPs.

No firm internal commitment for funding of trials from DOH units and counterpart funding from IHPs is not secured, then sponsorship by DOH is not feasible from the outset

IX. SEPARABILITY CLAUSE

If any portion or provision of this Order is declared invalid or unconstitutional, the validity and enforceability of the remaining portions or provisions shall not be affected thereby.

X. EFFECTIVITY

This Joint Administrative Order shall take effect after fifteen (15) days following its publication in a newspaper of general circulation and upon filing with the University of the Philippines Law Center of three (3) certified copies of this Order.

FRANCISCO T. DUQUE III, MD, MSc
Secretary

Annex A. Basic requirements for the Application of Ethical Clearance

- Review Application Form
- Protocol Summary Sheet
- Sites where the protocol will be implemented
- CVs of the coordinating PI and site PIs
- Research Protocol
- Versions of informed consent forms (including those translated in the local language)
- Recruitment and advertisement materials
- Investigator brochure
- Other protocol-related documents

Reference: Department Circular No. 2017-0354. *Single Joint Ethics Review Standard Operating Procedures.* (October 30, 2017). Department of Health.

Annex B. Non-Disclosure and Confidentiality Agreement

I,_____, an employee of the_____**,** and assigned as the_____for the project_____, is hereby legally bound, consents, and accepts the following obligations, terms and conditions as set forth in this Agreement in consideration of being granted *conditional access* to certain information that is owned by, produced by, or in the possession of the Department of Health (DOH), Philippines; and in compliance with the requirements of the DOH regarding confidentiality, privacy and security of information:

1. As used in this Agreement, *information* refers to confidential and/or sensitive information in which the loss of, misuse of, or unauthorized access to or modification can adversely affect the *national interest of the country, conduct of the DOH's programs*, or the *privacy* to which an individual is entitled. Confidential *information* is marked CONFIDENTIAL or unmarked CONFIDENTIAL but was declared confidential, and oral communications that have been declared CONFIDENTIAL by an Authorized Officer of the Department of Health (DOH);

2. I understand and accept that by being granted conditional access to *information*, confidence and trust are placed in me by the DOH and I am obligated to protect the *information* from unauthorized disclosure, in accordance with the terms of this Agreement and applicable laws, regulations, issuances and directives;

3. I have been informed that unauthorized disclosure, unauthorized retention, or negligent handling of *information* confidential information by me, may deprive the DOH, the rightful owner of the system of its intellectual property rights and could cause damage or irreparable injury to the Department and Government of the Philippines or could be used to the undue and unethical advantage of another nation/s or people such as myself and my company;

4. I shall not disclose or release *information* provided to me to anyone without proper authority or authorization from the DOH. Should there are situations that warrant the disclosure or release of *information*, I shall do so only under approved circumstances and in accordance with applicable laws, regulations or directives, and shall comply with any and all dissemination restrictions as required or relayed by the proper authority;

5. I shall not alter or remove markings which indicate a category of *information* or require handling instructions from any materials I may come in contact with, unless such alteration or removal is authorized by the DOH or consistent with applicable laws, regulations or directives;

6. Upon completion of my engagement as a/an_____under the project's contract, or completion of my work whichever occurs first, I shall return all *information* to which I have access or which are in my possession. Further, I shall surrender promptly to the DOH any documents whatsoever that are in my possession;

7. I solemnly swear that any *information* given to me shall remain confidential even after the completion of the project itself;

8. I shall not retain any documentation, source code or other *information* both in soft and hard copies used in this project;

9. I shall not modify, reverse engineer, decompile or disassemble any subsystems, modules, and/or software program codes, and sell to any government or private entities later the outputs of this project;

10. I shall promptly report to the appropriate DOH officials any loss, theft, misuse, misplacement, unauthorized disclosure, or other security violations in which I have knowledge of and whether or not I am personally involved.

11. Unless and until I am released in writing by the authorized personnel of the DOH, I understand that all conditions and obligations imposed upon me by this Agreement apply during the time that I am granted conditional access, and at all times thereafter;

12. If any provision of this Agreement is held to be invalid or unenforceable, all other provisions shall remain in full force and effect;

13. I am aware that violations of the terms and conditions of this Agreement may result in the cancellation of my conditional access to *information* or subjected to sanctions provided by pertinent laws and statutes of the Philippines.

IN WITNESS WHEREOF, I have hereunto set my hand this ___ day of _____ 202x in the City of Manila, Philippines.

Affiant

SUBSCRIBED AND SWORN to before me this_____day of_____202x, in the City of Manila, Philippines.

Notary Public

Doc. No._____;
Page No._____;
Book No._____;
Series of 202x.

Annex C. Algorithm for DOH Sponsorship

Annex D. References

[i] *GLOSSARY: Contract Research Organisation (CRO).* Pharma iQ. https://www.pharma-iq.com/glossary/contract-research-organisation-cro

[ii] *Guideline for Good Clinical Practice Integrated Addendum to ICH E6(R1): Guideline For Good Clinical Practice E6(R2).* Good Clinical Practice Network. https://ichgcp.net/introduction

[iii] Vijayananthan, A. et.al. (2008, January 11). The importance of Good Clinical Practice guidelines and its role in clinical trials. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3097692/pdf/biij-04-e5.pdf

[iv] *Guidance for Clinical Investigators, Sponsors, and IRBs. Adverse Event Reporting to IRBs – Improving Human Subject Protection.* (2009, January). Food and Drug Administration. https://www.fda.gov/media/72267/download