General Guidelines and Framework for Biobank and Associated Databases

Forthe Department of General Surgery 1 (GS 1) and the Department of Obstetrics and Gynecology (OB-GYN), University of the Philippines-Philippine General Hospital (UP-PGH)

1.) PURPOSE

This document describes the general guidelines for researchers at the Philippine General Hospital (PGH) and its affiliated institutions that collect and store human biological samples and/or associated data, for the purpose of medical research. These guidelines lay out general requirements for establishing, maintaining and providing access to biobanks and their associated databases.

2.) SCOPE

This procedure applies tobiospecimenobtained from Department of General Surgery 1 (GS 1) and Department of Obstetrics and Gynecology (OB-GYN), University of the Philippines-Philippine General Hospital (UP-PGH). Theguidelines cover research using the new and existing biobanks and associated databases at PGH and its affiliated institutions. Where the research use of previously approved biobanks is currently impracticable, grandfathering (i.e., allowing a pre-existing practice to continue) may be desirable following UP Manila Research Ethics Board (UPMREB) approval. Although these guidelines primarily target biobanks and associated databases that are part of observational studies, it should be noted that clinical trials are increasingly adding a biobanking component to the main study. Research projects that involve biobanking, but also interventions (such as study drugs or devices) are subject to additional requirements.

The Guidelines must be interpreted in light of existing national and provincial laws and ethical guidelines, with certain clarifications (National Ethical Guidelines For Health And Health-Related Research 2017). Specific policies and/or standard operating procedures ("SOPs") that address the issues outlined in these guidelines should be adopted. To ensure the research value and future interoperability of biobanks and associated databases, researchers should also follow international ethical norms and scientific best practices, where possible. PGH researchers who store data and samples in exterior locations or jurisdictions should consult these General Guidelines for Biobanks and Associated Databases, as their activities affect PGH and the medical research community as a whole. Finally, special considerations may apply with respect to data and samples collected from minors, incapable adults and deceased persons.

3.) RESPONSIBILITIES

3.1 It is the responsibility of the biobank director/s (Director of GS 1and OB-GYN) to maintain this procedure.The PGH director will oversee the biobank director/s, ensuringthat this procedure is

followed carefully. UPMREB will be the committee responsible for approving protocols related to the use and collection of the biobank and associated database. The PGH director will be responsible for the appointment of the Biobank Directors.

3.2 It is the responsibility of each clinical research associate (CRA) or thesample collection operator to understand the contents of this procedure and adhere to the procedure.CRAswill coordinate with the surgeons, consultants, and the biobank staff / encoder. CRAs will be hired under each biobank directors.

3.3 TheEncoder of the biobank registry will be the one responsible for the data provided by the CRA.

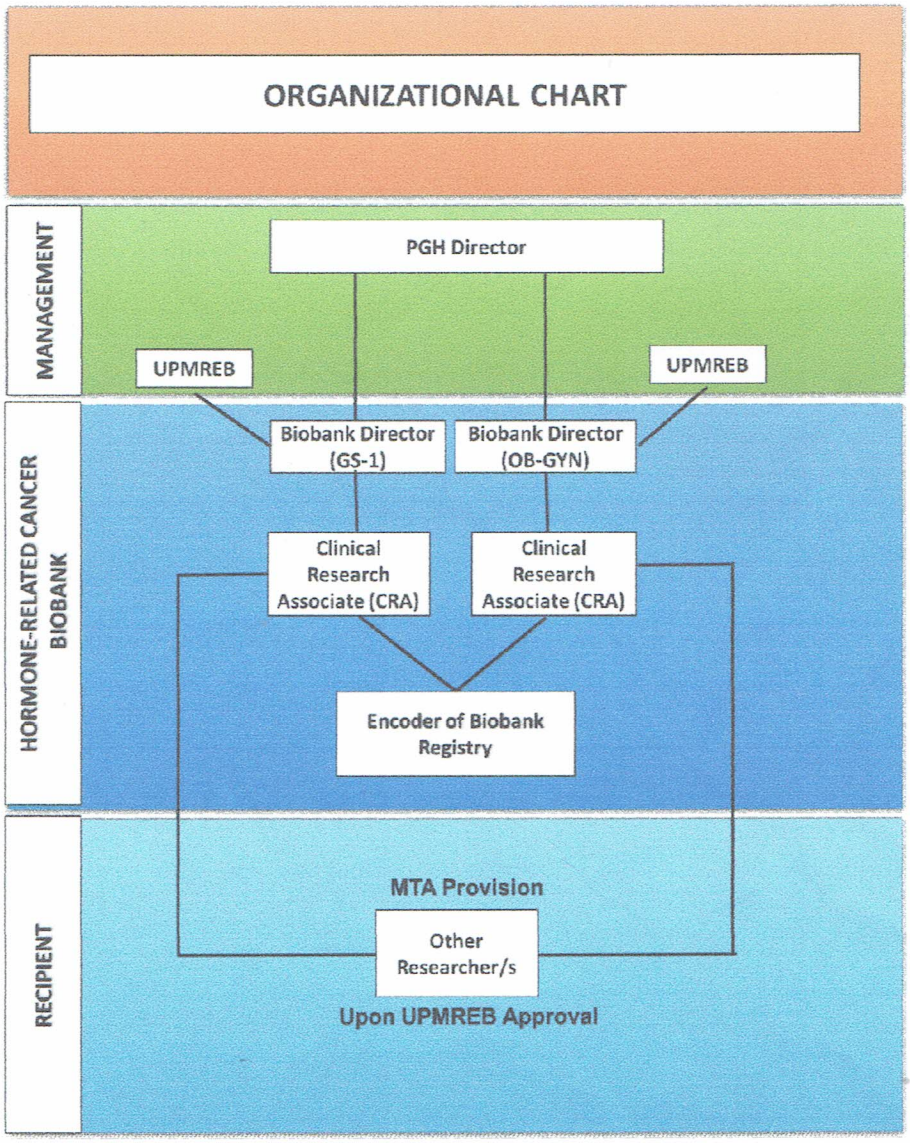

Figure 1. Summary of Organizational Chart of the PGH Biobank.

4.) OVERVIEW OF THE FRAMEWORK

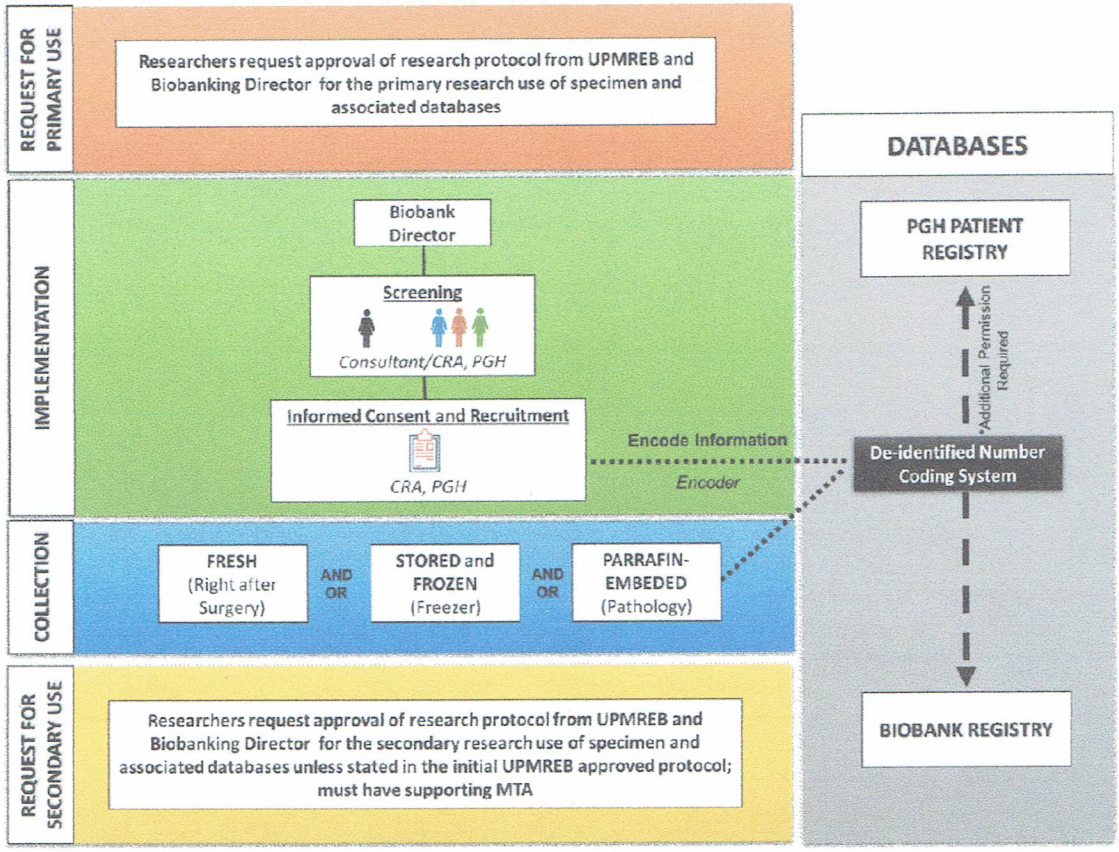

Figure 2. Overview of the Workflow of the PGH Biobank and Associated Databases

4.1 Request for the Primary Research Use of Human Biological Specimens. Researchers must request approval of the research protocol from**UPMREB** and **Biobanking Director** for the **primary research use of specimen and associated databases**. Most human biological specimens come fromsamples collected for diagnostic or therapeutic procedures, but other sources can includeautopsies, volunteer donors, or materials collected and shared by other researchers.The term "biospecimen" includessub-cellular components such as DNA or RNA, cells or tissues from any part of the human body, organs, bodily products such as hair, urine, etc., blood and blood fractions, saliva and buccal cells (Exceptions: Organisms, such as bacteria and viruses, isolated from human specimensare not human biological specimens)

4.2Implementation of the Biobank. An initial screening of patients will be done by the CRA and consultants.After confirming the diagnosis of the patient, an informed consent will be offered to the patients and/or volunteers. If they consented, sample collection will proceed.

4.3Collection and Storage of Biospecimens. Depending on the type ofspecimen, CRAs are usually given aliquots or sections of a specimen in a collectionand not the entire

specimen. The various formats for collecting and storing biospecimensinclude:aspirates, tissue culture, frozen samples, formalin-fixed or paraffin-embedded tissues, histological slides, and extracted DNA and RNA. For the purpose of this biobank, biobank specimen will be categorized as (a) fresh samples, (b) stored/frozen, and (c) paraffin-embedded. For fresh samples, biospecimens must be obtained as fresh as possible and must be coordinated with the Primary Researcher as indicated in their approved UPREB. For frozen samples, biospecimens must be kept in the freezer immediately. For paraffin-embedded samples,biospecimens may be obtained from the pathology department. Results must be coordinated by the CRA afterwards.

4.4Database and Information Management: This is crucial to track specimens and any associated data. Information is usually managed by agroup of specific data fields, such as,Specimen code/ID number, Specimen storage unit location, Specimen type, condition and amount, Diagnosis, Demographics, Histopathology, Patient treatment/outcome, Verification of informed consent, Donor restrictions on specimen use. This informationmust be stored in a secured biobank registry, different from the PGH Patient Registry. All information in the biobank registry must already be de-identified. Personal identifying data (direct identifiers) must not be stored in the biobank registry. Access and useof personal identifying data (e.g. names and addresses) from the PGH Patient Registry must be restricted and must be approved first by the UPREB.

The CRAs, encoders, and biobank director will manage human specimen data. Researchers who obtain specimens from tissue banks and repositories often receive samples with a "limited data set." This is to protect the identity of the subject/patient without compromising the goals of conducting meaningful research. A limited data set must have all the direct identifiers removed, such as: admission, discharge, and service dates; year of birth, and if applicable, death; age (including age 90 or over); and five-digit zip code or any other geographical subdivisions, such as state, county, city, precinct and their equivalent geocodes (except street address), treatment response and outcome data, family history information (i.e. cancer risk, gene mutation, etc.).

*Other investigators who would want access to "limited data set" should ask permission with the UPMREB and biobank director and must be legally and ethically obligated to protect data that is considered privateinformation.

4.5Request for Secondary Research Use of Human Biological Specimens. Researchers must obtain a separate approval of their research protocol from UPMREB and they must ask permission from the Biobanking Director for the use of specimen and associated databases.

5.) REFERENCE AND DOCUMENTS

National Ethical Guidelines for Health and Health-Related Research 2017

6.)DEFINITIONS AND ABBREVIATIONS

Access: access to Samples and/or Data for approved research purposes

Approved User: a researcher with appropriate institutional and ethics approvals that seeks to access Samples and/or Data.

Biobank: an organized collection of searchable Samples and/or associated Data stored for specific or as-of-yet unspecified research purposes.

Confidentiality: the duty to safeguard information provided in trust.

Controlled Access Dataset: composite health data that are associated with a unique, but not directly identified. Participant.

Data: information about a Participant provided to a Biobank (usually through questionnaires, linkages to registries, and/or morbidity/administrative Databases), including any medical images or information generated from the analysis of Participant Samples (e.g. personal, medical, genetic, genomic or proteomic information).

Database: an organized collection of searchable Data associated with a Biobank and stored for a specific or as-of-yet unspecified research purpose. Databases may be established as part of a research project, or as a resource/infrastructure for access by other researchers. They may contain Data collected directly from Participants, or repurposed from existing research, clinical, or administrative Databases.

General Research Results: aggregate results drawn from the analysis of Data and Samples of a group of research Participants.

Identifiability: there are five levels of Identifiability of Samples and associated Data:

Directly identifying information: information that identifies a specific individual through direct identifiers (e.g., name, social insurance number, personal health number).

Indirectly identifying information: information that can reasonably be expected to identify an individual through a combination of indirect identifiers (e.g., date of birth, place of residence or unique personal characteristic).

Coded information: information that has been stripped of direct and indirect identifiers, which have been replaced with a numerical code. A list that links the identifiers to the coded information is retained and is kept secure, to allow re- identification of Participants in certain circumstances.

Anonymized information: information that is irrevocably stripped of any direct or indirect identifiers, and for which no code is kept that allows for future reidentification.

Anonymous information: information that has never been associated with direct or indirect identifiers (e.g., anonymous surveys).

Incidental Findings ('IFs'): findings generated during the course of research that may or may not be clinically significant and/or are medically actionable, but go beyond the aims and

objectives of the study.

Individual Research Results ('IRRs'): findings generated during the course of research that have potential health importance for a Participant.

Governance: policy orientation and management that guides and monitors research activities, ensuring that they respect ethical, legal and scientific norms.

Director or Manager (of the Biobank): a person or organization that manages the Biobank and has the overall responsibility for staff, for communicating with researchers, and for reporting to institutions or agencies. The Manager is the custodian ofData and Samples, and is responsible for their security and ethical use throughout the lifecycle of the Biobank.

Open Access Database: a Database that usually contains aggregate Data and is publiclyaccessible.

Participant: an individual (patient or healthy volunteer) who contributes Samples and/or Data to a research project and/or study.

Privacy: the right of an individual to be free from intrusion or interference by others, or to choose to be identifiable to others.

UPM Research Ethics Board ('UPMREB'):University of Manila Research Ethics Board idthe board or committee constituted of health professionals and non-medical members to review the ethical acceptability of research involving humans conducted within UPM-PGH and its affiliated institutions. This is officially recognized by PHREB.

Samples: all human biological materials, including tissues, organs, blood, plasma, skin, serum, DNA, RNA, proteins, cells, hair, nail clippings, urine, saliva and other bodily fluids. Biological materials related to human reproduction are subject to additional requirements beyond the scope of these Guidelines.

Secondary Use: the use of Samples or Data in a way that differs from the original purpose of their collection.

7.) Custodianship

The biobank director of UPM-PGH is the custodian that have the continuing obligations to ensure, among other things, the long-term physical integrity of Samples; the Privacy and Confidentialityof Participants; as well as the use, storage, distribution, and disposal of Samples and Data.

8.) Governance

External Governance / Compliance

PGH and its affiliated institutions should ensure that the Biobank and associated Databases comply with external sources of Governance, including laws, codes, institutional policies, and funding agency ethics requirements. For external governance and compliance, Biobanks and associated Databases should also undergo review and approval by **UPMREB,**

biobank director and must also respect the **National Guidelines**.

Internal Governance

PGH and its affiliated institutions are responsible to ensure that the Biobank and its associated Databases have appropriate internal Governance. For the internal governance, **PGH Director**outlines leadership, management of operations, recruitment, re-contact and access processes, and may be subject to review by an UPMREB or other external body. The roles and the individuals or committees who will perform them should be clearly defined. Two particularly important roles are operations management and oversight of access. Operations management of the PGH Director establishes and oversees standards for the operations of the Biobank and associated Databases, including standard operating procedures, quality control, quality assurance, and data protection policies used when handling and storing Samples and Data. In turn, access is governed by an access policy and in some cases a separate committee. In some situations, an access agreement may be signed that limits the use of Samples and Data to approved purposes, ensures confidentiality, and clarifies any publication policies and downstream intellectual property rights, etc. Other internal Governance roles include communications and the establishment of ethical/legal, and scientific advisory positions.

9.) Collection of Samples and Data / Recruitment

The UPMREB should review and approve the establishment of a Biobank and associated Databases before Participants are recruited. Even where Data alone is collected, and there is little interaction with Participants or risk to their bodily integrity, UPMREB review is required. The UPMREB should ensure that the basic elements of a Governance framework are in place. The scope of research activities, potential privacy risks, and future access approval systems should also be put in place before recruitment, so they can be appropriately reflected during the consent process. Biobanks and associated databases should carefully consider any special issues relating to the participation and inclusion of vulnerable populations. In all cases, the means used to solicit a participant should not undermine the voluntary quality of consent. Participants should neither be unduly induced nor over-solicited. The UPMREB should keep in mind how the proposed procedures will affect the scientific validity and integrity of the proposed research.

9.) Secondary Research Use of Samples or Data

UPMREB approval is required for the use of already existing research Samples and Data in ways that differ from the original purpose of their collection. In addition, re-consent may be required unless waived by the UPMREB. Ensure that a supporting MTA is provided.

10.) Consent

Research involving the collection of Samples and Data requires both UPMREB review and the consent of the Participant donating the Samples and Data. Consent should be given in writing, unless the circumstances justify otherwise (e.g., illiteracy; ethics approved electronic format; linguistic issues, etc.). Many normative documents describe the contents of informed consent. These Guidelines cover issues specific to Biobanks and associated Databases. Despite the complex administrative, scientific, and ethical nature of biobanking, care should be taken by Biobanks and associated Databases and UPMREBs to ensure that the consent process is neither incomprehensible nor prohibitively long. Associated standard operating procedures or policies should be reviewed by the UPMREB along with the consent form.

11.) The Right to Withdraw and its Modalities

Participants have a right to withdraw from research at any time, even verbally. Researchers should ensure that Participants understand this right, and provide a simple way of exercising it, including control over future use and/or destruction of Samples or Data. This right, procedures for its exercise, and any limitations posed to it by Data aggregation and anonymization or publication, should be clarified in the consent form. The following statement may be written in the inform consent:

You have the right to withdraw from the project any time without fear of compromising your medical care. If you want to leave the project, please call us at [number of the biobank director]. We will get from you further instructions regarding any further use of your sample and medical information. Additionally, you may opt for following options, just tick the necessary box:

- ☐ *No further use of your biospecimens;*
- ☐ *No further use of your medical information;*
- ☐ *No further contact from the project staff;*

12.) Confidentiality and Privacy

Biobanks and associated Databases should ensure that appropriate safeguards (physical, administrative, and technical) are in place to protect the identity of Participants to the degree desired, to clearly identify the individuals authorized to access personal information (including access from outside researchers), and to identify and plan for situations where linkage has been consented to. REBs should ensure that each of these aspects is addressed.

13.) Storage

Storage of samples will be as approved by the UPMREB. Furthermore, the biobanks and

associated Databases "shall ensure that they have or use appropriate facilities, equipment, policies and procedures to store human biological materials safely, and in accordance with applicable standards". Security mechanisms that prevent non-authorized persons from accessing Samples and Data are to be implemented (i.e., coding, double-coding, encryption, scrambling, anonymization, lock and key, etc.). The code should only be accessible to authorized individuals, and only in those situations foreseen in the consent.

14.) Access

Any access to and use of samples and data should be consistent with the Participant's original consent, or should be foreseen by law. Access procedures should be clearly described in the UPMREB approved research protocol.These procedures may involve the establishment of a committee or officer in charge of reviewing access requests and verifying researcher bona fides. The committee includes the PGH director and the UPMREB.For biobanks and associated Databases planning to share Samples and Data with outside researchers, same approval is needed to accomplish.It is the responsibilities of outside researchers to limit use to approved purposes, to protect Samples and Data from unauthorized access, and to not attempt re-identification should be outlined in a legally binding access agreement.

15.) Commercialization

The Biobank and associated Databases, Participants, and researchers should all understand who may have rights in any possible, eventual commercial applications or intellectual property ("IP") generated. Generally, Participants do not receive any eventual intellectual property rights. This should be clearly stipulated in the consent form. Approved Users can develop commercial applications and IP via contractual arrangements. The Biobank should clearly state any limitations or privileges relating to IP as a condition of Access.

16.) Dissemination

Participants should not be identified in academic publications stemming from biobanking activities. This should be explained during the consent process, and should be stipulated as a condition for any publications by Approved Users. To ensure proper recognition of funders, Data providers. Managers, procedures and Participants, the Biobank and its associated Databases may also request proper attribution, as a condition of access, in publications by Approved Users.

17.) Deceased Individuals

Legal representatives should respect the wishes of deceased individuals, as expressed

during their lifetime. If there is no such indication, legal representatives should act in accordance with the interests of deceased individuals. Samples removed during routine medical care can be used with the consent of the person who could have given consent to the care required by the state of health of the individual while alive.

18.) Feedback to Participants

General Research Results: The names of projects and researchers using Samples and Data, along with information in lay language, on the general progress or on aggregate results should be made available to Participants on a publicly accessible website, or by other means and sent to them upon request.

Individual Research Results and Incidental Findings: The consent form should identify whether or not IRRs and/or IFs will be returned to Participants, and the conditions and procedures for such return. The UPMREB should review the plan for such return. It will depend to a large extent on the purpose, structure, and particular population of the Biobank and its associated Databases. In addition, the research protocol determines what information is collected and how it is analyzed, and therefore determines the likelihood that the research may reasonably generate findings that are scientifically valid and of clinical utility to individuals. Other conditions include their vulnerability and dependence, whether a clinical relationship already exists, the intensity and duration of their interactions, and, the availability of adequate funding, personnel, and validation or re-identification technologies.

If warranted, IRRs and/or IFs concerning Participants who are minors, incapable adults or deceased individuals should be returned to their legal representatives. All decisions concerning medically actionable results should be taken in the best interests of minors and incapable individuals.

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