INVESTIGATOR HANDBOOK

Phoebe Putney Memorial Hospital, Inc.

Institutional Review Board

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TABLE OF CONTENTS

Chapter 1 – INTRODUCTION

Phoebe Putney Memorial Hospital, Inc. Institutional Review Board ("IRB") is responsible for determining whether proposed research is scientifically valid and the anticipated benefits to the subjects as well as the knowledge that is expected to be gained outweigh the risks.

The IRB operates in compliance with:

- Protection of Human Subjects (DHHS), 45 CFR 46
- FDA Regulations on Human Subjects Research, 21 CFR 50 and 56
- Phoebe Putney policies and procedures

In accordance with the policy "Institutional Review Board Jurisdiction and Authority", the IRB shall have the authority and responsibility to:

a. Approve, require modifications in, or disapprove all research activities that fall within its jurisdiction. If a protocol is disapproved, the applicant has the right to appeal the decision to the IRB for reconsideration. Administrative approval may not be given for research that has been disapproved by the IRB.
b. Suspend or terminate research that is not being conducted in accordance with applicable laws and IRB or PPMH policies, or that has been associated with unexpected serious harm to subjects.
c. Provide ongoing oversight of approved research studies, which may include, but is not limited to: conducting audits, investigating complaints, reviewing reported protocol deviations and/or reports of scientific misconduct, and requiring third-party verification.
d. Ensure prompt reporting to the FDA and other authorities, as appropriate, of: (1) any unanticipated problems involving risks to subjects or others; or (2) any instance of serious or continuing noncompliance by an investigator; or (3) any suspension or termination of IRB approval. [See related PPMH policy, "External Reporting"]
e. Request any documentation and information it deems necessary beyond the protocol and sample informed consent form, such as budgets and grant applications. The IRB will notify all investigators via email or other method of the requested documentation.

The IRB reviews and monitors research involving human subjects. The term "Human Subject" (or Participant) is defined as:

> "A living individual about whom an investigator (whether professional or student) conducting research obtains:
>
> (1) data through intervention or interaction with the individual, or
> (2) identifiable private information."
>
> **Intervention** includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject of the subject's environment that are performed for research purposes.
>
> **Interaction** includes communication or interpersonal contact between investigator and subject.

Private Information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

Please consult the IRB's Human Subjects Research policy for additional information.

The IRB has the authority to approve, require modification in, or disapprove research. The purpose of the IRB review is to assure, both in advance and by periodic review, that appropriate steps are taken to protect the rights and welfare of humans participating as subjects in research. To accomplish this purpose, the IRB typically uses a group process to review research protocols and related materials. The IRB is responsible for approving what constitutes an adequate informed consent confirming that all necessary elements of informed consent are included. It also reviews the credentials and medical licenses of potential Principal Investigators. The IRB requires continuing education for Principal Investigators and their staff, IRB members and administrative staff to ensure appropriate training in human research subject protections.

This handbook outlines the responsibilities of the Principal Investigator and should be read by the key personnel on the research team. We look forward to working with you to ensure the safeguarding of the rights, privacy and welfare of those who volunteer to participate in research studies.

The IRB Mission Statement:

The mission of Phoebe Institutional Review Board is to protect the rights, privacy, and welfare of human subjects who volunteer to participate in research studies.

Chapter 2 – THE BELMONT REPORT

(Ethical Principles and Guidelines for the Protection of Human Subjects of Research)

The Belmont Report is the cornerstone statement of the ethical principles upon which the federal regulations for protection of human subjects are based. The IRB recommends that all Principal Investigators and key research personnel read the introductory guidance below and the Belmont Report. *The following is taken from the Office of Human Research Protection Institutional Review Board Guidebook. http://www.hhs.gov/ohrp/archive/irb/irb_guidebook.htm*

On September 30, 1978, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research submitted its report entitled "The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research." The Report, named after the Belmont Conference Center at the Smithsonian Institution where the discussions which resulted in its formulation were begun, sets forth the basic ethical principles underlying the acceptable conduct of research involving human subjects. Those principles, respect for persons, beneficence, and justice, are now accepted as the three quintessential requirements for the ethical conduct of research involving human subjects.

- **Respect for persons** involves recognition of the personal dignity and autonomy of individuals, and special protection of those persons with diminished autonomy.
- **Beneficence** entails an obligation to protect persons from harm by maximizing anticipated benefits and minimizing possible risks of harm.
- **Justice** requires that the benefits and burdens of research be distributed fairly.

The Report describes how these principles apply to the conduct of research. Specifically, the principle of respect for persons underlies the need to obtain informed consent; the principle of beneficence underlies the need to engage in a risk/benefit analysis and to minimize risks; and the principle of justice requires that subjects be fairly selected. The Report also provides a distinction between clinical practice and research. The text of the Report is thus divided into two sections: (1) boundaries between clinical practice and research; and (2) basic ethical principles. The full text of the Report, which describes each of the three principles and its application, is provided as Appendix D to this handbook.

A.) Boundaries Between Clinical Practice and Research

While recognizing that the distinction between research and therapy is often blurred, clinical practice is described as interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of clinical or behavioral practice is to provide diagnosis, preventive treatment, or therapy to particular individuals. The Commission distinguishes research as designating an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective. The Report recognizes that experimental procedures do not necessarily constitute research, and that research and clinical practice may occur simultaneously. It suggests that the safety and effectiveness of such experimental procedures should be investigated early, and that institutional oversight mechanisms, such as clinical practice committees, can ensure that this need is met by requiring that major innovations be incorporated into a formal research project.

B.) Applying the Ethical Principles

1.) Respect for Persons:

Required by the moral principle of respect for persons, informed consent contains three elements: information, comprehension, and voluntariness. First, subjects must be given sufficient information on which to decide whether to participate, including the research procedure(s), their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw from the research at any time. Responding to the question of what constitutes adequate information, the Report suggests that a reasonable volunteer standard be used: "the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation." Incomplete disclosure is justified only if it is clear that: (1) the goals of the research cannot be accomplished if full disclosure is made; (2) the undisclosed risks are minimal; and (3) when appropriate, subjects will be debriefed and provided the research results.

Second, subjects must be able to comprehend the information that is given to them. The presentation of information must be adapted to the subject's capacity to understand it; testing to ensure that subjects have understood may be warranted. Where persons with limited ability to comprehend are involved, they should be given the opportunity to choose whether to participate (to the extent they are able to do so), and their objections should not be overridden, unless the research entails providing them a therapy unavailable outside of the context of research. Each such class of persons should be considered on its own terms (e.g., minors, persons with impaired mental capacities, the terminally ill, and the comatose). Respect for persons requires that the permission of third persons also be given in order to further protect them from harm.

Finally, consent to participate must be voluntarily given. The conditions under which an agreement to participate is made must be free from coercion and undue influence.

2.) Beneficence:

Closely related to the principle of beneficence, risk/benefit assessments are concerned with the probabilities and magnitudes of possible harms and anticipated benefits. The Report breaks consideration of these issues down into defining the nature and scope of the risks and benefits, and systematically assessing the risks and benefits. All possible harms, not just physical or psychological pain or injury, should be considered. The principle of beneficence requires both protecting individual subjects against risk of harm and consideration of not only the benefits for the individual, but also the societal benefits that might be gained from the research.

In determining whether the balance of risks and benefits results in a favorable ratio, the decision should be based on thorough assessment of information with respect to all aspects of the research and systematic consideration of alternatives. The Report recommends close communication between the IRB and the investigator and the IRB’s insistence upon precise answers to direct questions. The IRB should: (1) determine the validity of the presuppositions of the research; (2) distinguish the nature, probability and magnitude of risk, with as much clarity as possible; and (3) determine whether the

investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.

Five basic principles or rules apply when making the risk/benefit assessment: (1) brutal or inhumane treatment of human subjects is never morally justified; (2) risks should be minimized, including the avoidance of using human subjects if at all possible; (3) IRBs must be scrupulous in insisting upon sufficient justification for research involving significant risk of serious impairment (e.g., direct benefit to the subject or manifest voluntariness of the participation); and (4) the proposed informed consent process must thoroughly and completely disclose relevant risks and benefits.

3.) Justice:

The principle of justice mandates that the selection of research subjects must be the result of fair selection procedures and must also result in fair selection outcomes. The justness of subject selection relates both to the subject as an individual and to the subject as a member of social, racial, sexual, or ethnic groups.

With respect to their status as individuals, subjects should not be selected either because they are favored by the researcher or because they are held in disdain (e.g., involving undesirable persons in risky research). Further, social justice indicates an order of preference in the selection of classes of subjects (e.g., adults before children).

Investigators, institutions, or IRBs may consider principles of distributive justice relevant to determining the appropriateness of proposed methods of selecting research subjects that may result in unjust distributions of the burdens and benefits of research. Such considerations may be appropriate to avoid the injustice that arises from social, racial, sexual, and cultural biases institutionalized in society.

Subjects should not be selected simply because they are readily available in settings where research is conducted, or because they are easy to manipulate as a result of their illness or socioeconomic condition. Care should be taken to avoid overburdening institutionalized persons who are already burdened in many ways by their infirmities and environments. Nontherapeutic research that involves risk should use other, less burdened populations, unless the research directly relates to the specific conditions of the class involved.

Chapter 3 – CATEGORIES OF RESEARCH REVIEW

A.) Full Board Review:

The IRB will conduct a full board review of all research involving more than minimal risk to human subjects. Specifically, this will include all research not described in the categories for exempt or expedited review.

The IRB uses a Primary Reviewer System for full IRB reviews at initial IRB review. Under this System, studies will be assigned in advance to two IRB members who shall conduct a full review of all materials using the provided IRB Reviewer Checklist.

Any issues that may be identified prior to the meeting by the Primary Reviewers should be conveyed to the Principal Investigator. If this is an oncology study, the Principal Reviewer will be referred to the Director of Clinical Research and Research Data Coordinator to be communicated to the Principal Investigator of the Cancer Center.

During the IRB Meeting, the Primary Reviewers take the lead for the overview and discussion of the study. Upon conclusion of the discussion, the IRB may take any of the following actions:

- Approve
- Approve with Minor Modifications
- Table
- Disapprove

The IRB may not approve a research study for more than one year. However, at the time of initial review or during any continuing review period the IRB can set a more frequent review interval for any study that it determines warrants more frequent review. Such determinations may be based on the initial risk and benefit factors, the investigator's experience, and new findings, knowledge or adverse effects that come to light during the course of the study.

Refer to the Phoebe Initial Review and Primary Reviewer System Policy on the Phoebe website for more detailed information. The website link is https://www.phoebehealth.com/about-us/institutional-review-board-(irb)

B.) Expedited Review:

Federal regulations recognize that certain aspects of research may be reviewed by an IRB through an expedited review procedure (45 CFR 46.110) (21 CFR 56.110). Expedited Review is a procedure through which certain kinds of research may be reviewed and approved without convening a meeting of the IRB when the study involves no more than minimal risk to the subjects.

Minimal Risk is defined as "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." (45 CFR 46.102(i))

Expedited Review may also be used for minor changes being made in previously approved research during the period for which approval is authorized. For purposes of this section, "minor changes" means any change in the materials or related documents of a research study that (a) would not affect the IRB's assessment of risks and benefits to subjects; (b) is a specified change in wording that has been agreed to by the IRB; or (c) is a change or clarification that has been specifically described by the IRB.

Expedited review may be performed by the IRB Chair, Vice Chair, or by one or more of the experienced IRB members designated by the IRB Chair. The results must be reported at a convened IRB meeting.
In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that they may not disapprove the research. A research study may be disapproved only after full board review.

The Principal Investigator will be notified by the IRB Administrator of the Expedited Review decision once it has completed the review process.

Refer to the Phoebe Expedited Review Policy on the Phoebe website for more detailed information. The website link is *https://www.phoebehealth.com/about-us/institutional-review-board-(irb)*

C.) Human Subject Research/Non-Human Subject Research Determination

The PPMH IRB has the sole authority to determine whether an activity meets the definition of "Human Subject Research". When activities are conducted that might represent "Human Subject Research", the activities must be submitted to the IRB for a determination.

Investigators do not have the authority to make an independent determination and must submit an "IRB Determination Form" to the IRB. An Investigator may request a determination that an activity is "Non-Human Subject Research," but the final determination will be made by the IRB. The IRB will make a determination whether an activity is "Human Subject Research" by considering whether the activity either:

1. Meets the regulatory definitions of "research" that involves "human subjects," or
2. Meets the regulatory definition of "clinical investigation."

Research involving cadavers must be submitted to the PPMH IRB and the IRB will determine which studies qualify as a "non-human subject."

Please refer to the Phoebe Human Subjects Research Policy for more detailed information.

D.) Exempt Human Subject Research.

Certain types of human subject research that present little or no risk to the participants may be classified as exempt from the federal regulations (45 CFR 46.101(b)) (21 CFR 56.104).

Exempt human subject research needs to fall into one of the exempt review categories which is outlined in the Exempt Review Policy. Only qualified IRB staff members are authorized to determine the eligibility for exempt status. Investigators are not authorized to make this determination. Please refer to the Exempt Review policy for specific details regarding exempt review.

The IRB Chairman or designee will determine whether the research meets the exempt criteria, based on the Criteria outlines in the Exempt Review policy and a review of the correspondence concerning the request, protocol, and associated documents. The decision will usually be communicated to the Principal Investigator upon completion of the review of the information submitted.
Refer to the Phoebe Exempt Review Policy on the Phoebe Website for a list of approved Exempt Review categories and more detailed information. The website link is https://www.phoebehealth.com/about-us/institutional-review-board-(irb)

Chapter 4 – PRINCIPAL INVESTIGATOR RESPONSIBILITIES

A.) Study Conduct:

The Principal Investigator is responsible for the ethical conduct of the research study, and for protecting the health and welfare of all subjects enrolled at his/her site(s). The clinical research study must be conducted as stated in the protocol and in accordance with all applicable federal, state and local laws and good clinical practices. It is expected that the Principal Investigator has the resources necessary to protect human participants, including:

- Sufficient time to conduct and complete the research.
- Adequate number of qualified staff members.
- Adequate facilities.
- Availability of medical or psychological resources that participants may need as a consequence of the research.
- A process to ensure that all persons assisting with the research are adequately informed about the protocol and their research-related duties and functions.
- Access to a population that will allow recruitment of the necessary number of participants.

The Principal Investigator should be familiar with the appropriate use of the investigational product(s), as described in the protocol, in the investigator's current brochure, in the product information and in other information sources provided by the sponsor. Furthermore, it is expected that the Principal Investigator follows the study's randomization procedures, if any, and that they ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the Principal Investigator should promptly document and explain to the sponsor any premature unblinding. The Principal Investigator is also responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

B.) Training and Education / Investigator and Study Staff Qualifications:

The Principal Investigator and all key research personnel should have appropriate training in conducting clinical trials and each should be aware of the obligations to communicate with the IRB and the sponsor during the study. The IRB requires that all Principal Investigators and any of their staff members assisting in the study must do the following;

1. Read the IRB Handbook and provide a signed attestation form to the IRB Coordinator.

2. Complete ethics training and provide a copy of the Ethics training certificate to the IRB Coordinator.

One option for Ethics training is via web-based modules on human subject protections provided by NIH Office of Extramural Research "Protecting Human Research Participants" training at the following web address https://phrp.nihtraining.com/users/login.php. (You will need to register prior to beginning the course.)

The Principal Investigator is responsible for providing evidence of his or her qualifications through an up-to-date curriculum vitae or other relevant documentation requested by the sponsor, the IRB, or the regulatory authority. The curriculum vitae or other relevant documentation for sub-investigators may be requested by the IRB on a case by case basis.

While the Principal Investigator is ultimately responsible for the conduct of the research study, the Principal Investigator may delegate research responsibility to appropriately qualified persons. However,

they must maintain oversight and retain ultimate responsibility for the conduct of those to whom they delegate responsibility. If a Principal Investigator will be unable to maintain primary oversight during a leave of absence, a change in principal investigator must be reviewed and approved by the IRB prior to the absence.

Further, the Principal Investigator is responsible for maintaining a list of appropriately qualified persons to whom they have delegated significant trial-related duties.

C.) Record Keeping:

The study records need to be retained as directed by the IRB, the sponsor and as required by applicable law and/or regulation. The Principal Investigator is responsible to maintain complete and accurate records for the following:

- Source records for each subject
- All correspondence with the sponsor and IRB including, but not limited to, copies of the application, notices of approval, acknowledgements, and signed informed consent documents

When investigators who have been designated to retain records on behalf of the institution leave that institution, the investigators and the institution should identify the successor responsible for maintaining those institutional records, either at the original institution or wherever the records are relocated.

Please refer to the Phoebe IRB Record Keeping Policy and the Principal Investigator Record Keeping Responsibilities Policy for the number of years the research materials must be maintained and any additional required recordkeeping responsibilities.

D.) Audits and Inspections:

All records of human subject research are subject to inspection by regulatory agencies, the sponsor and the IRB. The IRB also has the authority to conduct for cause and/or random audits of investigative sites under its review. The IRB or an independent third party may observe the implementation and conduct of human subject research activity under the IRB's review, including observance of the informed consent process, at any time.

The IRB may conduct random audits on active protocols. Investigators will receive notice two weeks in advance of the scheduled audit. The Principal Investigator is responsible for being prepared at all times for an audit or inspection.

E.) Referral Fees, Incentives, and Bonus Payments for Recruitment:

1.) Referral Fees:

The IRB does not support the recruitment of research subjects by payment to the Principal Investigator, Sub-Investigator, Clinical Coordinator(s), or other healthcare professionals for patient referrals. This is in accordance with the American Medical Association Code of Medical Ethics which states, "Physicians may not accept payment referring a patient to a research study" and "Physicians should not accept payment solely for referring patients to research studies"; the World Medical Association

International Code of Medical Ethics which states, “A physician shall not receive any financial benefits or other incentives solely for referring patients”; and the American College of Physicians Ethics Manual which states, “Giving or accepting finder’s fees for referring patients to a research study generates an unethical conflict of interest for physicians”. In addition, state law may prohibit such practices. Payment to subjects for referring others may be considered by the IRB on a case-by-case basis.

Please refer to the Institutional Review Board Payments to Subject policy for additional information.

2.) Incentives and Bonus Payments for Recruitment: Fees paid based on the timing or rate of participant enrollment is prohibited unless they are judged not to interfere with providing prospective participants with sufficient opportunity to consider whether to participate and do not increase the possibility of coercion or undue influence on the Principal Investigator or participants. The Principal Investigator should report to the IRB any proposed incentives, gifts, or bonus payments to the Principal Investigator or study staff other than the original contractual agreement for review. These will be reviewed on a case by case basis. The IRB is concerned that these practices may cause undue influence on the research staff. *See AMA Code of Medical Ethics 7.1.4 Conflicts of Interest in Research*

F.) Summary of Requirements of the Principal Investigator:

The Principal Investigator is required to provide the following information and reports to the IRB. These requirements should be reviewed by all individuals involved in the research activities. If you have any questions, please contact the IRB and we will be glad to assist you.

- **Amendments:** Once a study has received initial IRB approval, any change to the study is considered an amendment. All amendments must be submitted to the IRB for review and approval prior to implementation, unless to eliminate immediate hazards to subjects, in which case the IRB must be notified immediately. All amendments must be submitted on the IRB Amendment/Modification Request Form.

- **Informed Consent:** All changes to the informed consent are considered an amendment to the study and must be reported to the IRB on the IRB Amendment/Modification Request Form. Approval must be granted by the IRB prior to use of the revised informed consent.

- **Advertisements and Recruitment Material:** These items are reviewed in accordance with FDA guidelines, and must be approved by the IRB prior to use. These items must be submitted with the IRB Application for Initial Review Form. Once an Investigator has received initial IRB approval, any advertisements and recruitment materials submitted for approval thereafter are considered amendments and must be accompanied by a completed IRB Amendment/Modification Request Form. Forms can be found on the IRB’s portal at phoebehealth.com.

- **Reportable Events:** Protocol Deviations, Serious Adverse Events, Unanticipated Problems, External Adverse Events, Sponsor-Granted Exceptions and Others as described in Chapter 7.

- **Continuing Review Reports:** In order for the study to continue after the first year, the Investigator must receive an annual continuing review approval prior to the study expiration date listed on the initial or renewal approval documents. The Investigator should submit the Continuing Review Request Form not less than one month prior to the last IRB meeting preceding the expiration date. Federal regulations do not allow the IRB to grant extensions or grace periods, so timely submission of the Continuing Review Request Form is important to avoid unnecessary interruptions in the study.

  A reminder will typically be sent prior to the due date, but it is the Principal Investigator's responsibility to ensure that all required continuing review reports are timely submitted. The Principal Investigator must submit to the IRB the following documents for the protocol to be considered for continuing review:

  - Continuing Review Request Form;
  - Status report on the progress of the research and findings obtained thus far (including the number of subjects enrolled to date);
  - Summary of any relevant recent literature;
  - Amendment/Modification Request Form (if applicable);
  - Current Informed Consent Form;
  - Annual safety summary report (detailed listing of all safety reports received during the past year), if applicable;
  - Relevant multi-center reports;
  - Study Protocol which includes all modifications previously approved by the IRB; and
  - Adverse Event Form, if applicable.

- **Site Final Report**: After the last subject has completed the study and the Sponsor has indicated that the study is completed at the site, the Application for Final Study Closure or Suspension Form must be submitted to the IRB to ensure proper closeout. These reports should include the date that the final subject completed the study. These forms should also be filed in the event of cancellation, suspension or termination of a study.

- **Enrollment Closure (Study Closed to Accrual, due to the sponsor no longer enrolling patients to the study):** When the Principal Investigator identifies that a study is closed to enrollment and/or temporarily closed to enrollment, the Principal Investigator will submit the IRB Enrollment Closure form. If the study is temporarily closed to enrollment and has been re-opened to accrual, the Principal Investigator will notify the IRB.

Chapter 5 – SUBMISSIONS TO THE IRB

A.) New Study Submissions:

Principal Investigators are required to submit a completed Initial Review Form along with all required documents referenced on the form to the Phoebe IRB. Instructions for completing the form are self-contained. All forms and guides are located on the Phoebe website and can be filled in electronically. If there are any questions, our staff will be glad to assist you. The website link is https://www.phoebehealth.com/about-us/institutional-review-board-(irb)

B.) Amendments to Previously Approved Research:

Any change to previously approved research must be reviewed and approved by the IRB prior to implementation.

1.) Protocol Amendments - Submit the Amendment-Modification form along with the following attachments:

- Informed Consent Form(s), if applicable – include both draft Informed Consent Form with changes indicated ((i.e. highlighted, redlined, etc.) and clean version of the ICF.
- Study Protocol, if applicable – include both draft protocol with changes indicated (i.e. highlighted, redlined, etc.) and clean version of study protocol.
- Recruitment materials, if applicable.
- Revised HIPAA form, if applicable.
- Updated Investigator's Brochure, if applicable.
- Revised research materials (survey, questionnaires, instruments), if applicable.

Protocol amendments must receive IRB review and approval before they are implemented, unless an immediate change is necessary to eliminate an apparent hazard to the subjects. The IRB should be notified of this occurrence immediately. If an amendment requires changes to the informed consent document, please follow the directions listed in section 2, Revisions to the Informed Consent Document, below.

2.) Revisions to the Informed Consent Document.

Submit a completed Amendment-Modification Form along with the required attachments referenced in the form.

3.) Changes to the Investigator's Brochure.

The Sponsor may update the Investigator's Brochure (IB) during the course of the study. Changes to the IB should be submitted to the IRB using the Amendment-Modification Form. If this is a multi-site study, the Sponsor will usually submit the revision on behalf of all the Principal Investigators participating in the study. Acknowledgement of receipt of the IRB will be provided.

4.) Change in Principal Investigator.

When there is a change of Principal Investigator for an already approved study, the following is required to be submitted to the IRB for review of the new Principal Investigator:

- Amendment/Modification Request Form
  - Note: this form may be used only if the new Principal Investigator will continue to conduct the study using only the procedures already approved, at only the site(s) already approved.
- CV of the new Principal Investigator (unless the CV has been submitted to the IRB within the last 2 years)
- Copy of the new Principal Investigator's DEA registration, if applicable
- Copy of ethics training certificate

5.) Change in Co-Investigator(s).

When there is an addition or removal of a Co-Investigator(s) for an already approved study, the following is required to be submitted to the IRB:

- The applicable section of the Amendment/Modification Request Form
- CV of the new Principal Investigator (unless the CV has been submitted to the IRB within the last 2 years)
- Copy of the new Principal Investigator's DEA registration, if applicable
- Copy of ethics training certificate

Please note: In general, if an individual is directly involved in the performance of procedures required by the protocol, and the collection of data, this person should be considered a co-investigator.

6.) Change in Site or Adding Additional Sites.

When there is a change in site location or additional sites are added, the following is required to be submitted to the IRB: Amendment/Modification Request Form for each site that has changed or been added to the study.

Refer to the Research Revisions and Amendments policy for further information.

7.) Translations for Subject Information and Informed Consent.

Non-English-speaking subjects will not be excluded from research that may have potential benefits. Investigators will plan for populations that are likely to be recruited into the study and translations will be incorporated into the study design to allow for appropriate recruitment and enrollment. Justifications for exclusion of non-English speakers must be included in the IRB application.

Subjects who do not speak English must have all written documents written in their native language to include an IRB approved consent document translated into the subject language by a certified translator (certification documentation is required). The subject must be given

a copy of the translated Informed Consent. An interpreter in the subject's native language must assist with the discussion. Please note: ad hoc translation may not replace the written document.

All Investigators are required to obtain a translated written consent document in a language understandable to the subject or the subject's legally authorized representative (LAR) if non-English speaking subjects will be participating in the study.

Refer to the IRB Non-English-Speaking Subjects policy for more information and specific details regarding requirements for Non-English-Speaking Subjects.

8.) Advertisements and Recruitment Materials.

Any advertisements and recruitment materials must be submitted to the IRB. Advertisements and recruitment materials submitted for review after the Investigator has received initial approval are considered amendments and must be accompanied by a completed Amendment/Modification Form.

Advertising or recruiting for study subjects are considered to be the start of the informed consent process. The information contained in the advertisement/recruitment materials and the mode of communication must be reviewed by the IRB and approved before they are used. All submitted materials must comply with applicable federal regulations, and state and local laws. Furthermore, it is the IRB's expectation that the recruitment processes which are employed by the Principal Investigator and the research staff are fair and equitable.

Please refer to the Subject Recruitment and Review of Advertisements Policy on the Phoebe IRB Website.

9.) Screening Questionnaires.

The IRB requires that any patient screening questionnaire include the following information:

- For telephone screenings, the prospective subject must provide their permission for the screening to proceed and for the screener to collect confidential medical information (otherwise, the screening should be ended)
- The prospective subject will be told that the information gathered from the screening procedure will be kept confidential
- The prospective subject will be told what will happen to the information collected (i.e. stored in a database)
- The prospective subject will be told what will be done with the information if he/she does not qualify for this study (i.e. will the information be destroyed, or, with the permission of the prospective subject, will the information be kept in a database and used for another study. In the latter case, the prospective subject must give his/her permission for the information to be stored)
- For telephone screenings, the prospective subject must be told that he/she does not have to answer any questions they do not want to respond to, and may choose to end the screening at any time

If Protected Health Information ("PHI") is to be recorded into a database, the Principal Investigator will need to complete and submit a Request for Waiver of HIPAA Authorization. The completed Application should be submitted along with the screening questionnaire for approval.

10.) Study Materials.

All materials that will be used as part of a study must be reviewed and approved by the IRB prior to use. These materials can be submitted as part of the initial study protocol; however, many times these materials are not available at the time of the initial submission. Materials which are submitted following initial approval of a study must be submitted as an amendment on the Amendment/Modification Form.

C.) Generic Materials.

Revisions to approved generic materials must be reviewed and approved before use. Approval of generic materials is valid for one year. Expired generic materials should not be used.

D.) Forms.

The IRB Forms are located on the Phoebe website www.phoebehealth.com under the IRB portal.

E.) Criteria for IRB Approval of Research.

Minimal Criteria for Approval of Research

In order for a research project to be approved, the IRB shall determine all of the following requirements are satisfied:

a. Risks to subjects are minimized. (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
b. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.
c. Selection of subjects is equitable, taking into account the purposes of the research study and the setting in which it will be conducted and being particularly cognizant of the special problems of research studies involving vulnerable populations.
d. Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by appropriate state and federal regulations. [See related PPMH policy "Informed Consent"]
e. Informed consent will be appropriately documented as required by state and federal guidelines.
f. Where appropriate, the research study makes adequate provision for monitoring the data collected to ensure the safety of subjects.

g. Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
h. Appropriate additional safeguards have been included to protect the rights and welfare of subjects who are likely to be vulnerable to coercion or undue influence.

F.) Notification of Approvals and Acknowledgements.

Notice of Decision. The IRB may take any of the following actions:

a. Approve
b. Approve with Minor Modifications
c. Table
d. Disapprove

All IRB decisions will be documented in the meeting minutes in accordance with the IRB Recordkeeping policy. The PPMH signatory official will be provided with minutes of all IRB meetings.

The IRB may not approve a research study for more than one year. However, at the time of initial review or during any continuing review period the IRB can set a more frequent review interval for any study that it determines warrants more frequent review. Such determinations may be based on the initial risk and benefit factors, the investigator's experience, and new findings, knowledge or adverse effects that come to light during the study.

Chapter 6 – CONTINUING REVIEW

Continuing review of IRB approved research is required under 45 CFR 46.109(e) and/or 21 CFR 56.109(f). IRB Studies must be reviewed annually.

Continuing IRB review is required as long as the research remains active for long-term follow-up of subjects or where the remaining research activities are limited to data analysis. If an IRB study was approved via Expedited Review, then the continuing review will also be done via Expedited Review. If the Study was approved by a full IRB Board review, then the annual review will also need to go to the full IRB Board for review and approval.

Investigators must submit a IRB Continuing Review Request Form and shall include the number of subjects enrolled to date and summarize the progress of the research and findings obtained thus far; the annual safety summary report (detailed listing of all safety reports received during the past year for the study), and any relevant recent literature, amendments or modifications to the research since the last review to the IRB Coordinator.

The IRB Continuing Review Request Form will outline all documents required to be submitted to the IRB for Continuing Review.

A.) Continuing Review Status Report: (Application for Continuation).

The IRB is required to review all non-exempt research projects at intervals appropriate to the degree of risk, but not less than once a year. All non-exempt research projects will receive full Board continuing review. It is the responsibility of the IRB to perform a substantive continuing review and consider the same issues as during initial review.

It is the Principal Investigator's responsibility to submit the Continuing Review Request Form in sufficient time to permit review and approval prior to the study expiration date. The regulations make no provision for any grace period extending the conduct of research beyond the expiration date of IRB approval. Continuing review and reapproval of research must occur on or before the one-year anniversary of the initial IRB approval date. To assist in this Principal Investigator obligation, the IRB Coordinator will typically send reminder notices (via e-mail), however it is the responsibility of the Principal Investigator to ensure the Continuing Review Request form is submitted to the IRB in a timely manner to prevent the study from expiring . It is important to remember that the IRB needs to receive the Continuing Review Report in sufficient time for review and re-approval of the research prior to the study expiration date. The Continuing Review Request form is located on the Phoebe IRB Website.

Refer to the Continuing Review Policy for more information.

Failure to submit Continuing Review Request Form prior to the expiration date of the Study.

If the Principal Investigator does not submit the IRB Continuing Review Request Form in time for the IRB review prior to the expiration date, he/she will be notified by phone and email that the IRB approval has expired

The continuation of research after expiration of IRB approval is a violation of federal regulations. Extensions beyond the expiration date will not be granted.

If the IRB has not reviewed and re-approved a research study by the study's current expiration date, IRB approval has expired and research activities, including subject accrual, must cease. Continuation of research interventions or interactions with subjects already enrolled should only continue when the IRB finds that it is in the best interest of the subjects to do so.

Refer to Chapter 12 of this handbook for more information regarding the Expiration of IRB Approval.

B.) Final Report.

After the last subject has completed the study and the Sponsor has indicated that the study is completed at the site, the Principal Investigator must submit a Site Final Report to the IRB to ensure proper closeout.

For more information regarding the Closure of Studies and submission of a Final Report to the IRB refer to Chapter 14 of this handbook.

Chapter 7 – REPORTABLE EVENTS

Many types of events must be reported to the IRB. In general, events that are unanticipated and increase the risk to subjects or others, which may significantly affect the conduct of the clinical trial, could affect a participant's willingness to continue in the study. A subject's noncompliance must be reported to the IRB.

It is the IRB's responsibility to determine whether or not an event is an unanticipated problem involving risk to subjects or others and to notify the investigator of what steps, if any, are necessary to continue the study. If the IRB determines that the event represents an unanticipated problem involving risk to subjects or others, the Principal Investigator, Sponsor, and applicable regulatory agencies will be notified within 10 business days. The IRB's Adverse Event policy provides in part as follows:

Definitions:

Adverse Event:

An Adverse Event is any experience or abnormal finding that has taken place during the course of a research project and was harmful to the subject participating in the research, or increased the risks of harm from the research, or had an unfavorable impact on the risk/benefit ratio, that was temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. Note that the Food and Drug Administration (FDA) also includes in its definition abnormal preclinical or laboratory findings which may not yet have resulted in direct harm to subjects (e.g. a bacteria is identified in a culture from the same batch of cells used to produce a vaccine which has been administered, even if no cases of infection have been reported).

Serious Adverse Event (SAE).

Any experience occurring that results in any of the following outcomes: death; life-threatening experience; requires in-patient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of these outcomes.

Unanticipated Problems.

Include any incident, experience, or outcome that meets **all** of the following criteria:

i. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
ii. Related **or** possibly related to participation in the research (*possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

iii. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Unanticipated Adverse Event.

Any Adverse Event occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is **not** consistent with either:

i. The known or foreseeable risk of Adverse Events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or

ii. The expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the Adverse Event.

1.) Internal Adverse Events.

Internal Adverse Events are adverse events that occur in a study that has been approved by the Phoebe Putney Memorial Hospital IRB at a site for which a Phoebe Putney Memorial Hospital Investigator is responsible for the conduct of the study.

All Internal Adverse Events that are determined by the principal investigator to be (i) serious and unanticipated; and (ii) occurred at a site under the purview of the IRB, must be reported by the Principal Investigator to the IRB, or notification of its occurrence, by electronically submitting the Adverse Event /Unanticipated Problem Report Form within 48 hours of the event .

The IRB Chair or designee will review reports of Adverse Events. Reports of all Internal Adverse Events that are serious and unanticipated will also be reviewed by the full IRB.

If the Principal Investigator believes a change in the protocol or consent documentation is warranted, he/she will submit an IRB Amendment/Modification Request Form. The IRB Chair or designee will forward the modification for appropriate review (i.e., expedited review if the change(s) is/are minor or full IRB review if the change(s) is/are substantive).

If the Principal Investigator has indicated that no change is required and the IRB disagrees, the Principal Investigator will be asked to submit a modification.

Reports of Internal Adverse Events that are not serious and unanticipated will be reported in summary form at the time of continuing review.

2.) External Adverse Events.

External Adverse Events are adverse events occurring in a study or site for which a Phoebe Putney Memorial Hospital investigator is not responsible for the conduct of the study.

All external Adverse Events that are determined by the principal investigator to be (i) serious and unanticipated; (ii) possibly related to study procedures; (iii) occurred at a site that is not under the purview of the IRB and/or the study is open to enrollment, or if patients are enrolled at our site; (iv) the study is open to enrollment or we have patients enrolled at our site, must be reported to the IRB within 5 business days of notification. A detailed Adverse Event/Unanticipated Problem Report Form must be submitted within 5 business days of the event of the investigator being notified. The IRB Chair or designee will review the report of Adverse Events or Unanticipated Problems.

Reports of all External Adverse Events that are Serious, Unanticipated, and possibly related to the study will also be reviewed by the full IRB.

In filing the report, the Principal Investigator must make the preliminary determination whether revision(s) to the protocol and/or consent document(s) is/are necessary. If a change is required, an Amendment/Modification Request Form must be submitted.

The IRB Chair or designee will forward the amendment for appropriate review (i.e., expedited review if the change(s) is/are minor or full IRB review is the change(s) is/are substantive).

If the Principal Investigator has indicated that no change is required and the IRB disagrees, the Principal Investigator will be asked to submit a modification.

Reports of External Adverse Events that are not Serious, Unanticipated and possibly related to the study will be reported in summary form at the time of continuing review.

3.) Unanticipated Problems.

Unanticipated Problems Include any incident, experience, or outcome that meets **all** of the following criteria:

i. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

ii. Related **or** possibly related to participation in the research (*possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

iii. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

All Unanticipated Problems must be reported promptly to the IRB via submission of an Adverse Event/ Unanticipated Problem Report Form.

A detailed Adverse Event/Unanticipated Problem Report must be submitted electronically within five (5) business days of the event or notification, whether the problem was internal or external. The IRB Chair or designee will review all reports of Unanticipated Problems and make a determination of whether additional review by the full IRB is required.

In filing the report, the Principal Investigator must make the preliminary determination whether a revision(s) to the protocol and/or consent document(s) is/are necessary. If a change is required, an IRB Amendment/Modification Request Form must be submitted promptly.

The IRB Chair or designee will forward the modification for appropriate review (i.e., expedited review if the change(s) is/are minor or full IRB review is the change(s) is/are substantive).

Reports of Unanticipated Problems that do not involve risks to subjects or others will be reported by the Principal Investigator in summary form at the time of continuing review.

4.) Other Adverse Events/Unanticipated Problems.

A summary of Adverse Events and Unanticipated Problems that occur during the approved study period must be submitted with other required materials at the time of continuing review. The summary for each type of adverse event should include, at a minimum:

- Number of subjects who experienced the event;
- Investigator's determination of whether or not the event is serious;
- Investigator's determination of the event's relationship to the study procedures (e.g., definitely, probably, possibly, probably not, definitely not related)

5.) Data Safety and Monitoring Board ("DSMB") Reports.

All DSMB reports that the investigator receives should be promptly reported to the IRB and submitted to the IRB.

6.) Report to Institutional Officials.

All Unanticipated Problems involving risks to subjects or others must be reported promptly to the IRB via submission of an Adverse Event/ Unanticipated Problem Report Form. When such reports are made regarding external Unanticipated Problems, the PPMH institutional officials who shall review such reports are the IRB Chair and IRB Staff.

When such reports are made regarding internal Unanticipated Problems, the IRB Staff shall promptly provide a copy of the Adverse Event/Unanticipated Problem Report to the Chief Operating Officer for PPMH.

7.) Report to Office for Human Research Protections ("OHRP").

Unanticipated Problems occurring in research covered by a Federalwide Assurance (FWA) must be reported by the IRB to the supporting, U.S. Department of Health & Human Services agency head (if applicable) and Office for Human Research Protections (OHRP).

This requirement applies only to **internal Unanticipated Problems.** The IRB Chair and IRB Staff will evaluate all reported internal Unanticipated Problems for possible reporting to OHRP, and the IRB Staff shall be responsible for making such reports in accordance with OHRP rules and regulations.

Please refer to the Adverse Events and Unanticipated Problems Reporting Policy for further information.

Chapter 8 – INFORMED CONSENT

A.) The Process of Consent and Assent.

All informed Consent Statements must be approved by the IRB prior to the initiation of the investigation of a drug, device, or behavioral research protocol. As a general rule, an Investigator must obtain an Authorization from all research subjects prior to the internal use or external disclosure of Protected Health Information (PHI) for any research related purpose that is not otherwise permitted or required as stated in the PPMH Policy for HIPAA Compliance in Research.

It is the responsibility of the investigator to assure that informed consent is received and properly distributed before the study begins. Only the most recent IRB approved informed consent form, date stamped by the Phoebe IRB with an expiration date, may be used to obtain consent from prospective subjects. Any changes or revisions to an approved version of the informed consent must be IRB approved prior to use. [See related PPMH policy "Research Revisions and Amendments" for more information]

Informed Consents must include several elements and in addition there are documentation requirements associated with the use of the Informed Consent.

For detailed information on what needs to be included in the Informed consent, please refer to the IRB Informed Consent Policy and the IRB Informed Consent Checklist under the forms section on the Phoebe IRB Website.

B.) Waiver of Informed Consent.

The Food and Drug Administration and the Office for Human Research Protections have regulations permitting a waiver of the general requirements for informed consent for certain research settings involving risks to subjects that are greater than minimal. The intent of the regulations is to allow research on life-threatening conditions for which available treatments are unproven or unsatisfactory in situations in which it is not possible to obtain informed consent.

The situations to which the regulations apply are limited to cases in which subjects cannot give consent and for whom a legally authorized representative cannot be located by the time the intervention must be used to be effective. Refer to Supplemental Form B – Request for Waiver of Informed Consent on the Phoebe IRB Website.

Chapter 9 - Waivers or Alterations of the Authorization Requirements to Use or Disclose Protected Health Information

A.) Introduction.

For some types of research, it is impracticable for researchers to obtain written authorization from research participants to use or disclose the participant's protected health information ("PHI"). To address this type of situation, the Privacy Rule 45 CFR 164.512 contains criteria for waiver or alteration of the authorization requirement by an IRB. Under the Privacy Rule, the IRB may waive or alter, in whole or in part, the Privacy Rule's authorization requirements for the use and disclosure of PHI in connection with a particular research project.

B.) Waiver in Whole.

A waiver in whole occurs when the IRB determines that no authorization will be required for a Principal Investigator to use or disclose PHI for a particular research project because certain criteria set forth in the Privacy Rule have been met. For example, if a study involved the use of PHI pertaining to numerous individuals where contact information is unknown, and it would be impracticable to conduct the research if authorization were required, the IRB could waive all of the authorization requirements for research participants if the IRB determines that all of the Privacy Rule waiver criteria had been satisfied. If the IRB approves such a waiver, the receipt of the requisite documentation of the approval permits a Principal Investigator to use or disclose PHI in connection with a particular research project without authorization. A partial waiver of the authorization requirements of the Privacy Rule might be requested, for instance, to allow a researcher to obtain PHI as necessary to recruit potential research subjects. For example, even if the IRB does not waive the authorization requirement for the entire research study, the IRB may partially waive the authorization requirement to permit a covered entity to disclose PHI to a researcher for the purposes of contacting and recruiting individuals into the study.

C.) Waiver in Part.

The IRB may also approve a request that removes some, but not all, required elements of an authorization. For example, the IRB may alter the authorization to remove the element that describes each purpose of the requested use or disclosure where, for example, the identification of the specific research study would affect the results of the study. Before a Principal Investigator could use or disclose PHI pursuant to the altered authorization, however, it must receive documentation that the IRB determined that all of the Privacy Rule waiver criteria at 45 CFR 164.512(i)(2)(ii) had been satisfied. Any subsequent use or disclosure of PHI by a Principal Investigator for a different research study would require an additional authorization, except as permitted without authorization under section 164.512(i) (e.g., with a waiver of authorization) or 45 CFR 164.514(e) (i.e., as a limited data set with a data use agreement).

D.) <u>Waiver Approval</u>.

The Privacy Rule establishes the criteria to be evaluated by the IRB in approving an authorization waiver or alteration. The criteria for IRB waiver or alteration of the authorization are consistent with the criteria for IRB waiver of the informed consent requirements contained in the Health and Human Services Protection of Human Subjects Regulations. For a Principal Investigator to use or disclose PHI under a waiver or an alteration of the authorization requirement, the Principal Investigator must submit to the IRB a completed Form H, Request for Waiver of HIPAA Authorization. The Principal Investigator must receive documentation of, among other things, the IRB's determination that the following criteria have been met:

- The PHI use or disclosure involves no more than minimal risk to the privacy of individuals based on at least the presences of (1) an adequate plan presented to the IRB to protect PHI identifiers from improper use and disclosure; (2) an adequate plan to destroy those identifiers at the earliest opportunity, consistent with the research, absent a health or research justification for retaining the identifiers or if retention is otherwise required by law; and (3) adequate written assurances that the PHI will not be reused or disclosed to any other person or entity except (a) as required by law, (b) for authorized oversight of the research study, or (c) for other research for which the use or disclosure of the PHI is permitted by the Privacy Rule.
- The research could not practicably be conducted without the requested waiver of alteration.
- The research could not practicably be conducted without access to and use of the PHI.

Chapter 10 – VULNERABLE POPULATIONS

A.) Vulnerable Populations.

The IRB does not allow research of any kind to be conducted on the following vulnerable populations:

- Pregnant women
- Fetuses
- Neonates, either viable or nonviable
- Children under the age of 18
- Prisoners
- Mentally disabled
- Economically or educationally disadvantaged

Please refer to the IRB Policy: Vulnerable Populations in Research.

Chapter 11 – RESEARCH CONFLICTS

A. Conflict of Interest.

Situations arise in which financial or other personal situations may compromise, or have the appearance of compromising, an investigator's professional judgment in conducting and reporting research. PPMH researchers are expected to perform their duties without having their loyalty divided or compromised.

The evaluation for assessing a potential bias to the mandate of human subject protections is very important. The principal investigator (PI) will certify to the following at the time of initial and each continuing review period on behalf of himself/herself as well as all research team members who may be in a position to influence the design, conduct or reporting of the research ("covered individuals"):

- we have read and understand PPMH's Financial Conflict of Interest policy; and
- have made all financial disclosures required by it, if any; and
- will comply with any conditions or restrictions imposed by the IRB or PPMH to manage, reduce, or eliminate actual or potential conflicts of interest.

The PI will also complete a PPMH IRB "Financial Conflict of Interest Disclosure Form" on behalf of himself/herself and all covered individuals of the research team. If there is a conflict or potential conflict, the PI will identity the conflicted member of the research team and attach any supporting documentation that further defines and/or explains the conflict or potential conflict.

IRB administrative staff will review all Disclosure forms to determine if a conflict or potential conflict has been disclosed. The IRB will review all disclosures to evaluate the extent of the potential conflict and determine whether the covered individual will be able to continue with the study or recommend other appropriate measures for reducing or managing the conflict. The IRB may also determine that the probability of the financial interest affecting the design, conduct or reporting of the research is too remote to warrant any specific conditions or restrictions or it may determine that monitoring procedures to be performed by external organizations are adequate to protect human subjects and the integrity and objectivity of the research.

Refer to the Phoebe IRB Financial Conflict of Interest Policy for definitions and details on what is considered a Financial Conflict of Interest.

If any information provided in the financial disclosure section changes during the course of the study, or within one year after the last participant completed the study as specified in the protocol, the IRB must be immediately notified.

The Principal Investigator has the responsibility to assess conflict of interest for each study and re- assess throughout the study. If conflict of interest becomes an issue, a report should be made to the IRB. The report should be accompanied by a plan for managing and minimizing the disclosed interests. Some possible actions that can be taken to manage potential conflicts include:

- Public disclosure of the significant conflict of interest
- Monitoring of the research by independent reviewers
- Modification of the research plan
- Divestiture of significant financial interests

The IRB has the final authority to decide whether the conflict and its management, if any, allows the research to be approved. Please note that failure to disclose possible conflicts of interest and/or failure to adequately manage the conflict is considered non-compliance with the requirements of the IRB.

For more information, Office of Human Research Protection ("OHRP") has published guidance for protecting research subjects from possible harm caused by financial conflicts of interest in research studies. The guidance document is entitled "Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection", (May 5, 2004). The target audience includes investigators, IRB members and staff, institutions engaged in human subjects research and their officials, and other interested members of the research community.

Chapter 12 – EXPIRATION OF IRB APPROVAL

The Principal Investigator holds the ultimate responsibility for tracking approval periods and ensuring that IRB approval does not expire. Failure to receive or notice IRB reminders does not absolve investigators of this responsibility, nor does it change the consequence of an expired approval.

A.) Expiration of IRB Approval.

1.) The IRB will notify the Principal Investigator when the documents necessary for the continuation of the study is due. Dates identified by the IRB are determined to allow for timely review of submitted materials as required for approval.

2.) It is the responsibility of the Principal Investigator to submit the Application for Continuing Review Request Form to the IRB prior to the expiration of the protocol. If the IRB has not approved the protocol by 12:00 AM (midnight) on the expiration date cited on the most recent Notice of IRB Approval, the IRB approval expires automatically.

3.) If an IRB approval expires, all research activities involving human subjects must stop. "All" includes, but is not limited to, subject contact, data collection, and data analysis. The IRB will notify the investigator of these requirements in writing upon expiration of approval.

- Even if the continuing review materials have been submitted to the IRB, all activities must stop until IRB re-approval is granted for the study.
- There is no "grace period" extending research activities beyond the expiration of IRB approval, even if the continuing review documents have been submitted.
- Activities that occur without a current IRB approval are considered non-compliant, with appropriate consequences.
- Retroactive approval for work done after the expiration date will not be granted.
- An expiration of IRB approval is not considered a suspension or termination of the study.

4.) If the Principal Investigator does not wish to continue the study past the expiration date, he/she must submit the Application for Final Study Closure Form to the IRB by the same date that continuing review documents are due. Choosing to close a study rather than pursue a continuing review does not extend the due date for submission of required materials.

Refer to the Expiration of IRB Approval and Subsequent Notice to Cease Study Activity Policy.

CHAPTER 13 – SUSPENSION OR TERMINATION OF IRB APPROVAL

A.) Suspension or Termination of IRB Approval.

The IRB has the authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements, or that has been associated with unexpected harm to subjects. If IRB approval is suspended or terminated, the IRB will:

- Consider actions to protect the rights and welfare of currently enrolled subjects.
- Consider whether procedures for withdrawal of enrolled subjects take into account their rights and welfare (e.g. making arrangements for medical care outside of a research study, transfer to another Principal Investigator, and continuation in the research under independent monitoring).
- Consider informing current subjects of the termination or suspension.
- Determine if any adverse events or outcomes have been reported to the IRB.

The IRB Chairman and Vice-Chairman are authorized to suspend or terminate research on an urgent basis for the imminent protection of human subjects. Any such actions will be reported and reviewed by the IRB.

DEFINITIONS.

Suspension - the IRB approval is suspended in whole (all research activities must stop) or in part (e.g. enrollment must stop) but allows for potential recommencement of the study. Suspended protocols are not closed with the IRB and require continuing review by the IRB.

Termination - IRB approval is terminated permanently, and the research activities cannot recommence at a later date. Terminated protocols are closed protocols, and they no longer require continuing review.

The Sponsor and appropriate regulatory agency will be notified within 10 business days of any determination made by the IRB to suspend or terminate approval of a research study or investigative site. The Principal Investigator will also be sent a letter within 10 business days detailing the IRB's determination, and the length of suspension or termination of IRB approval. Any response from the Principal Investigator, Sponsor or regulatory agencies will be reviewed by the IRB.

CHAPTER 14 CLOSURE OF IRB STUDIES

It is the IRB's expectation that all concluded studies will be officially closed with the IRB. The IRB considers a study concluded when the following conditions are met:

A.) A study should be finally closed by the PI when no further contact with human subjects or their individually identifiable information is planned; no subjects are or will be treated or followed; all data are gathered and analyzed; and any final reports are complete.

1.) The completion or final closure of a previously approved research protocol or project constitutes a change in activity that must be reported to the PPMH IRB.
2.) Subsequent use of any data from a finally closed project in a new study will require a new IRB submission.
3.) Study final closure is not a withdrawal. It does not refer to an investigator's or IRB's withdrawal of a submission from the IRB review process prior to IRB approval.
4.) Investigators should not finally close research which is "closed to enrollment", as this means only that no additional subjects will be enrolled in the study.

B. The PPMH IRB may finally close or suspend projects without PI approval in the following circumstances:

1.) If it is determined that the investigator is no longer affiliated with PPMH;
2.) In response to unanticipated problems involving risk to subjects or others, serious or continuing non-compliance, findings presented during an IRB review, or problems identified in a monitoring process;
3.) If the investigator has not responded to the IRB's requests for revisions and/or clarifications within a timeframe which is determined on a case-by-case basis, based upon the vulnerability of the subject population and the risk of research or if a study is not accruing participants.

When deciding if a study should be finally closed, the IRB considers, among other things:

a. The level of risk,
b. Possible benefit,
c. Funding source,
d. Value of the knowledge to be gained,
e. Possibility of remedy

C. Final closure or suspension of IRB-approved studies is reportable to institutional officials and to the appropriate regulatory authorities. Final closure of an expired study is not termination of approval of research per 45 CFR 46.113 and is not reportable. Failure to submit a closure form for all closed studies, including those that have expired or lapsed, may cause the IRB to postpone the review and approval of future research protocols.

D. Principal Investigator Responsibilities when closing an IRB Study.

There is a process that must be followed in closing a study with the IRB as well as certain forms that must be submitted. Refer to the IRB Closure of Studies Policy for the current process.

Chapter 15 – SPECIAL TOPICS

A.) HIPAA.

HIPAA stands for the Health Insurance Portability and Accountability Act of 1996. The Privacy Rule establishes the conditions under which certain healthcare groups, healthcare clearinghouses, organizations, or businesses, called "covered entities," handle the individually identifiable health information known as Protected Health Information (PHI). Principal Investigators should be aware of the Privacy Rule because it establishes the conditions under which covered entities can use or disclose PHI for research purposes. The specific regulations for HIPAA are found in: 45 CFR 160 and 164.

Covered entities are permitted to use or disclose protected health information for research with individual authorization, or without individual authorization under limited circumstances as set forth in the Privacy Rule.

Authorization by Research Participant:

HIPAA specifies that a covered entity may neither use nor disclose PHI for research purposes unless the patient has provided, in advance, his or her written authorization for such use or disclosure (unless a waiver is obtained). Authorization may be combined with the informed consent document. It is the responsibility of the PI to be aware of any state and local laws that raise the standard that HIPAA has set forth.

Six Required Elements:

- A description of the PHI to be used or disclosed that specifically identifies the information
- Name of the persons and/or entities authorized to use or disclose the PHI
- Name of the persons and/or entities authorized to receive the PHI
- The purpose of the requested use or disclosure of PHI
- An expiration date, which may be indicated as "end of study" or "none," for Authorization to place PHI in a research database
- Signature of the subject and date

Three Required Statements:

- A statement that the subject has the right to give written notice to withdraw their authorization at any time, including any applicable exceptions to the right to withdraw authorization
- A statement that once the subject's PHI has been disclosed, it is possible that the receiver may re-disclose the information for study purposes.
- A statement that informs the subject that they may choose to refuse to sign the authorization and this will not affect their medical treatment

General Requirements:

- The authorization must be written in plain language (approximately 8th grade level)
- A copy of the authorization form must be given to the subject

B.) EMERGENCY USE OF INVESTIGATIONAL DRUG OR DEVICE.

FDA and the IRB recognize that situations arise in which there could be a need to use an investigational drug, biologic, or device in a manner inconsistent with the approved protocol or by a physician who is not an investigator on the clinical study. The criteria for emergency use are defined in the Code of Federal Regulations (CFR) and must be followed. The emergency use provision in 21 CFR 56.104(c) is an exemption from prior IRB review and approval and may not be used unless all provisions of 21 CFR 56.102(d) exist. This exemption allows one use without prospective IRB review, and FDA requires that the IRB is notified within 5 working days of the emergency use of the test article. Any subsequent use requires prospective IRB review and approval.

OHRP regulations do not provide for an emergency use exception to IRB review, though OHRP regulations do allow physicians to provide emergency medical treatment to patients. In emergency use situations, OHRP regulations do not consider patients to be research subjects.

For approval of a test article's use in an emergency situation, a full IRB review is required (expedited or subcommittee review/approval is not allowed). However, if the conditions of 21 CFR 56.102(d) are met but it is not possible to convene a quorum within the time available, the IRB Chairman or appropriate designee (an IRB member with appropriate medical knowledge) may acknowledge notification of the emergency use.

The investigator seeking acknowledgement of emergency use of a test article should provide the IRB with a letter documenting the presence of each of the following conditions. This notification to the IRB must occur within 5 working days of use of the test article.

The IRB Chairman or appropriate designee will review the investigator's letter of notification, and will only acknowledge emergency use of a test article if each of the following conditions exist to justify the use:

a.) a life-threatening situation exists in which no standard acceptable treatment is available, and
b.) the test article must be used expeditiously, meaning insufficient time is available to convene a quorum for full-Board IRB review/approval.

If the IRB Chairman (or designee) confirms the presence of the necessary conditions, the IRB Chairman (or designee) will sign/send a letter to the investigator acknowledging notification of emergency use of the test article. If the Sponsor requires a written acknowledgement from the IRB in order to approve shipment of the test article, the IRB will provide the Sponsor a copy of its acknowledgement letter to the investigator.

Definitions:

Emergency Use means the use of a test article (e.g., investigational drug, biologic, or device) on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval (21 CFR 56.102(d). For the purposes of 21 CFR 56.102(d), "life-threatening" includes the scope of both life-threatening diseases/conditions and severely debilitating diseases/conditions.

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. 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 IRB is feasible.

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

There are many considerations regarding patient protections in emergency use. Please contact the IRB if you are contemplating emergency use of a test article.

C.) Humanitarian Use Device.

A Humanitarian Use Device (HUD) is a device intended to benefit patients by treating or diagnosing a disease that affects or is manifested in not more than 8,000 people in the United States per year. To be considered for HUD status, a device sponsor must submit a humanitarian device exemption (HDE) application to the FDA. The applicant must demonstrate that no comparable devices are available for the use intended for the device in question and that the applicant device could not be brought to market without the conditions of the HDE.

Role of the IRB:

This is the only situation where federal regulations require the IRB to approve and monitor an activity that is not considered research. The PI must submit the PPMH IRB Application for Humanitarian Use Device under an HDE Form to the IRB for review and approval along with other documents outlined in the IRB Humanitarian Use Device Policy. Upon initial approval from the IRB, the PI is responsible for submitting the IRB Continuing Review Request form annually to the IRB.

In addition, IRB approval is required for any modifications of the device and/or proposed clinical use of the device.

Refer to the Humanitarian Use Devices (HUD) policy for more information.

D.) Compassionate Use.

Compassionate use provisions allow access to the test article for subjects who do not meet the criteria for inclusion in an approved clinical trial. Subjects must have a serious or immediately life-threatening disease or condition, and the investigator must feel the deviation represents a benefit in treating and/or diagnosing their disease or condition. Prospective FDA, Sponsor and IRB approval is required prior to the use. Please contact the IRB to discuss a compassionate use request.

E.) Genetic Research.

Genetic research typically presents risks of social and psychological harm to participants rather than risks of physical harm. The Board will consider the following areas when reviewing a genetic testing protocol or sub-study:

- Selection of participants
- Confidentiality and privacy
- Disclosure of information
- Secure storage of data and biological samples
- Participant withdrawal (possible continued risk with long term storage of biological samples)
- Assessment of predictive value of the research study

CHAPTER 16 – OVERVIEW OF HOW TO SUBMIT A STUDY TO THE PHOEBE IRB FOR REVIEW AND APPROVAL

All research involving human subjects (participants) must be submitted to the Phoebe IRB Coordinator in a timely manner to be placed on the IRB Agenda for review and approval. Until you have received written notice that your research has been approved, you should not begin to collect data or interact with human subjects.

In determining the human research type, investigators should first read the Phoebe IRB policies for Exempt, Expedited and Full Review of Research. After reviewing the policies, if there is still a question, the investigator may consult with the IRB Administrator, Janine Sarti via email at jsarti@phoebehealth.com.

The IRB Administrator will make the final determination about review type, with consultation of the IRB Chairperson and appropriate members of the IRB, as needed.

Submission instructions, policies, forms and a Checklist of what to submit for each category of study (Exempt/Expedited or Full Board Review) may be found on Phoebe's IRB Website - https://www.phoebehealth.com/about-us/institutional-review-board-(irb). Refer to "Application Process and Deadlines."

Deadlines and Review Timing for New Study Submissions to the IRB

Review Type	Submission Deadline	Letter to PI announcing the IRB Decision
Full	1 week prior to the meeting – refer to the IRB Meeting Schedule on the Phoebe IRB Website for a specific date.	Within 7 business days after the IRB Committee Meeting.
Expedited	N/A	Within 1 week after receipt.
Exempt	N/A	Within 1 week after receipt.

Certain types of research may require the IRB to consult with an expert in a particular field (e.g. medical Specialist, pharmacist, registrar, etc.) These situations may require additional review time.

Continuing Review Deadlines and Review Timing for Active IRB Studies

Deadlines and turn around time are shown in the table below. Submissions must be complete at the time of receipt in order to meet the deadline. Submissions received after the close of business on the day of any deadline are subject to the next meeting or review cycle.

Review Type	Submission Deadline	Letter to PI announcing the IRB Decision
Full	Preferably two months prior to the expiration of the Study.	Within 7 business days after the IRB Committee Meeting.
Expedited	Preferably two months prior to the expiration of the Study.	Within 1 week after receipt.

IRB Fees

The Institutional Review Board charges for review of human subject research funded by private industry sponsors (predominately pharmaceutical or device manufacturing companies).

IRB Fees are not charged if:

1. The study is funded by the federal government or another non-profit entity; or

2. The study is investigator-initiated and unfunded;

These fees are charged to help offset the costs associated with scientific and ethical review, continuing review and document processing. IRB Fees are non-refundable and will be billed at the time services are completed. Refer to the Fee Schedule on the Phoebe IRB Website.

In exceptional circumstances, some studies may receive a waiver or discount of these fees. This will be based on the nature of the study and the extent of funding provided by the sponsor of the study. Examples where a waiver of fees may be appropriate include certain humanitarian device studies or expanded access and compassionate use studies where only minimal funding is provided by the sponsor. Fee waivers or discount requests will be reviewed on a case-by-case basis and will be determined by the IRB Administrator.

APPENDIX A – IRB POLICIES

IRB POLICIES

All IRB policies are located on the IRB portal on the Phoebe website. The website link is https://www.phoebehealth.com/about-us/institutional-review-board-(irb).

The following is a list of IRB policies

- Adverse Events and Unanticipated Risk Reporting Policy
- Allegations of Non-Compliance Concerns or Complaints
- Closure of Studies
- Continuing Review
- Emergency Use of Drugs Biologics and Devices
- Exempt Review
- Expedited Review
- Expiration of IRB Approval and Subsequent Notice to Cease Study Activity
- Financial Conflict of Interest
- Human Subjects Research Policy
- Humanitarian Use Devices (HUD) Policy
- Initial Review and Primary Reviewer System
- IRB Informed Consent
- IRB Jurisdiction and Authority
- IRB Membership
- IRB Record Keeping
- IRB Voting
- Non-English-Speaking Subjects
- Payment to Subjects
- Planned Emergency Research
- Research Revisions and Amendments
- Use of Non-Local IRBs

APPENDIX B - IRB FORMS

All IRB Forms are located on the IRB Portal on the Phoebe Website. The website link is https://www.phoebehealth.com/about-us/institutional-review-board-(irb).

- Adverse Event-Unanticipated Problem Report Form
- Amendment-Modification Form
- Application for Final Study Closure
- Application for Humanitarian Use Device under an HDE
- Continuing Review Request Form
- Determination Form
- Emergency Use Report Form
- Enrollment Closure Form
- Informed Consent Checklist
- Initial Review Form
- Protocol Closure or Suspension Form
- Protocol Deviation Report Form
- Request for Exemption
- Request to Re-open a Closed Study
- Supplemental Form A – Request for Waiver of Written Consent
- Supplemental Form B – Request for Waiver of Consent
- Supplemental Form C – Request for Deception in Research
- Supplemental Form D – Use of Internet in Research
- Supplemental Form E – Research involving Stored Data for Future Use
- Supplemental Form F – Research involving Cognitively Impaired Individuals
- Supplemental Form G – Financial Conflict of Interest Disclosure Form
- Supplemental Form H – Request for Waiver of HIPAA Authorization
- Supplemental Form I – Multiple Adverse Events Reporting Form
- Supplemental Form J – Additional Research Team Members Form

APPENDIX C - Certification

(To be completed by all persons involved in the research, including office staff.)

I hereby certify that I have read and understand the Phoebe Putney Memorial Hospital Institutional Review Board Handbook. I have been given the opportunity to ask questions. I agree to comply with the Handbook and all policies and procedures of the IRB. I understand if I do not comply with the requirements instituted by the IRB, that my research protocol may be suspended or terminated.

Agreed to and Accepted by
Principal Investigator:

By: _____
Signature

_____
Printed Name

Date: _____

Agreed to and Accepted by
Co- Principal Investigator, if applicable:

By: _____
Signature

_____
Printed Name

Date: _____

Agreed to and Accepted by
Co- Principal Investigator, if applicable:

By: _____
Signature

_____
Printed Name

Date: _____

APPENDIX C – Certification - Continued

(To be completed by all persons involved in the research, including office staff.)

I hereby certify that I have read and understand the Phoebe Putney Memorial Hospital Institutional Review Board Handbook. I have been given the opportunity to ask questions. I agree to comply with the Handbook and all policies and procedures of the IRB. I understand if I do not comply with the requirements instituted by the IRB, that my research protocol may be suspended or terminated.

Agreed to and Accepted by the following Office Staff that will be involved in the research:

Printed Name	Signature	Date

Printed Name	Signature	Date

Printed Name	Signature	Date

Printed Name	Signature	Date

Printed Name	Signature	Date

Return completed Certification Form to the IRB Coordinator: Denise Pardue at dpardue@phoebehealth.com.

APPENDIX D

THE BELMONT REPORT

THE BELMONT REPORT

Office of the Secretary

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

April 18, 1979

AGENCY: Department of Health, Education, and Welfare.

ACTION: Notice of Report for Public Comment.

SUMMARY: On July 12, 1974, the National Research Act (Pub. L. 93-348) was signed into law, there-by creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles. In carrying out the above, the Commission was directed to consider: **(i)** the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine, **(ii)** the role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects, **(iii)** appropriate guidelines for the selection of human subjects for participation in such research and **(iv)** the nature and definition of informed consent in various research settings.

The Belmont Report attempts to summarize the basic ethical principles identified by the Commission in the course of its deliberations. It is the outgrowth of an intensive four-day period of discussions that were held in February 1976 at the Smithsonian Institution's Belmont Conference Center supplemented by the monthly deliberations of the Commission that were held over a period of nearly four years. It is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects. By publishing the Report in the Federal Register, and providing reprints upon request, the Secretary intends that it may be made readily available to scientists, members of Institutional Review Boards, and Federal employees. The two-volume Appendix, containing the lengthy reports of experts and specialists who assisted the Commission in fulfilling this part of its charge, is available as DHEW Publication No. (OS) 78-0013 and No. (OS) 78-0014, for sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.

Unlike most other reports of the Commission, the Belmont Report does not make specific recommendations for administrative action by the Secretary of Health, Education, and Welfare. Rather, the Commission recommended that the Belmont Report be adopted in its entirety, as a statement of the Department's policy. The Department requests public comment on this recommendation.

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

Members of the Commission

Kenneth John Ryan, M.D., Chairman, Chief of Staff, Boston Hospital for Women.

Joseph V. Brady, Ph.D., Professor of Behavioral Biology, Johns Hopkins University.

Robert E. Cooke, M.D., President, Medical College of Pennsylvania.

Dorothy I. Height, President, National Council of Negro Women, Inc.

Albert R. Jonsen, Ph.D., Associate Professor of Bioethics, University of California at San Francisco.

Patricia King, J.D., Associate Professor of Law, Georgetown University Law Center.

Karen Lebacqz, Ph.D., Associate Professor of Christian Ethics, Pacific School of Religion.

**** David W. Louisell, J.D., Professor of Law, University of California at Berkeley.*

Donald W. Seldin, M.D., Professor and Chairman, Department of Internal Medicine, University of Texas at Dallas.

**** Eliot Stellar, Ph.D., Provost of the University and Professor of Physiological Psychology, University of Pennsylvania.*

**** Robert H. Turtle, LL.B., Attorney, VomBaur, Coburn, Simmons & Turtle, Washington, D.C.*

*** Deceased.

Table of Contents

Ethical Principles & Guidelines for Research Involving Human Subjects

Scientific research has produced substantial social benefits. It has also posed some troubling ethical questions. Public attention was drawn to these questions by reported abuses of human subjects in biomedical experiments, especially during the Second World War. During the Nuremberg War Crime Trials, the Nuremberg code was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This code became the prototype of many later codes [1] intended to assure that research involving human subjects would be carried out in an ethical manner.

The codes consist of rules, some general, others specific, that guide the investigators or the reviewers of research in their work. Such rules often are inadequate to cover complex situations; at times they come into conflict, and they are frequently difficult to interpret or apply. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted.

Three principles, or general prescriptive judgments, that are relevant to research involving human subjects are identified in this statement. Other principles may also be relevant. These three are comprehensive, however, and are stated at a level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in research involving human subjects. These principles cannot always be applied so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.

This statement consists of a distinction between research and practice, a discussion of the three basic ethical principles, and remarks about the application of these principles.

Part A: Boundaries Between Practice & Research

A. Boundaries Between Practice and Research

It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research. The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called "experimental" when the terms "experimental" and "research" are not carefully defined.

For the most part, the term "practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals [2]. By contrast, the term "research' designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.

When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental," in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this

description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project [3].

Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.

Part B: Basic Ethical Principles

B. Basic Ethical Principles

The expression "basic ethical principles" refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethics of research involving human subjects: the principles of respect of persons, beneficence and justice.

1. Respect for Persons. —

Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.

An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so.

However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated.

Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequence. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations.

In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. Whether to allow

prisoners to "volunteer" or to "protect" them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle of respect itself.

2. Beneficence. — Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence. The term "beneficence" is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: **(1)** do not harm and **(2)** maximize possible benefits and minimize possible harms.

The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person regardless of the benefits that might come to others. However, even avoiding harm requires learning what is harmful; and, in the process of obtaining this information, persons may be exposed to risk of harm. Further, the Hippocratic Oath requires physicians to benefit their patients "according to their best judgment." Learning what will in fact benefit may require exposing persons to risk. The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks.

The obligations of beneficence affect both individual investigators and society at large, because they extend both to particular research projects and to the entire enterprise of research. In the case of particular projects, investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures.

The principle of beneficence often occupies a well-defined justifying role in many areas of research involving human subjects. An example is found in research involving children. Effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children -- even when individual research subjects are not direct beneficiaries. Research also makes it possible to avoid the harm that may result from the application of previously accepted routine practices that on closer investigation turn out to be dangerous. But the role of the principle of beneficence is not always so unambiguous. A difficult ethical problem remains, for example, about research that presents more than minimal risk without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

3. Justice. — Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of "fairness in distribution" or "what is deserved." An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Another way of conceiving the principle of justice is that equals ought to be treated equally. However, this statement requires explication. Who is equal and who is unequal? What considerations justify departure from equal distribution? Almost all commentators allow that distinctions based on experience, age, deprivation, competence, merit and position do sometimes constitute criteria justifying differential treatment for certain purposes. It is necessary, then, to explain in what respects people should be treated equally. There are several widely accepted formulations of just ways to distribute burdens and benefits. Each formulation mentions some relevant property on the basis of which burdens and benefits should be distributed. These formulations are **(1)** to each person an equal share, **(2)** to each person according to individual need, **(3)** to each person according to individual effort, **(4)** to each person according to societal contribution, and **(5)** to each person according to merit.

Questions of justice have long been associated with social practices such as punishment, taxation and political representation. Until recently these questions have not generally been associated with scientific research. However, they are foreshadowed even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients. Subsequently, the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was condemned as a particularly flagrant injustice. In this country, in the 1940's, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. These subjects were deprived of demonstrably effective treatment in order not to interrupt the project, long after such treatment became generally available.

Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

Part C: Applications

C. Applications

Applications of the general principles to the conduct of research leads to consideration of the following requirements: informed consent, risk/benefit assessment, and the selection of subjects of research.

1. Informed Consent. —

Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied.

While the importance of informed consent is unquestioned, controversy prevails over the nature and possibility of an informed consent. Nonetheless, there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension and voluntariness.

Information. Most codes of research establish specific items for disclosure intended to assure that subjects are given sufficient information. These items generally include: the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Additional items have been proposed, including how subjects are selected, the person responsible for the research, etc.

However, a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided. One standard frequently invoked in medical practice, namely the information commonly provided by practitioners in the field or in the locale, is inadequate since research takes place precisely when a common understanding does not exist. Another standard, currently popular in malpractice law, requires the practitioner to reveal the information that reasonable persons would wish to know in order to make a decision regarding their care. This, too, seems insufficient since the research subject, being in essence a volunteer, may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hand of a clinician for

needed care. It may be that a standard of "the reasonable volunteer" should be proposed: the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation.

A special problem of consent arises where informing subjects of some pertinent aspect of the research is likely to impair the validity of the research. In many cases, it is sufficient to indicate to subjects that they are being invited to participate in research of which some features will not be revealed until the research is concluded. In all cases of research involving incomplete disclosure, such research is justified only if it is clear that **(1)** incomplete disclosure is truly necessary to accomplish the goals of the research, **(2)** there are no undisclosed risks to subjects that are more than minimal, and **(3)** there is an adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them. Information about risks should never be withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given to direct questions about the research. Care should be taken to distinguish cases in which disclosure would destroy or invalidate the research from cases in which disclosure would simply inconvenience the investigator.

Comprehension. The manner and context in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized and rapid fashion, allowing too little time for consideration or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice.

Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the presentation of the information to the subject's capacities. Investigators are responsible for ascertaining that the subject has comprehended the information. While there is always an obligation to ascertain that the information about risk to subjects is complete and adequately comprehended, when the risks are more serious, that obligation increases. On occasion, it may be suitable to give some oral or written tests of comprehension.

Special provision may need to be made when comprehension is severely limited -- for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as incompetent (e.g., infants and young children, mentally disable patients, the terminally ill and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving them the opportunity to choose to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm.

The third parties chosen should be those who are most likely to understand the incompetent subject's situation and to act in that person's best interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research as it proceeds in order to be able to withdraw the subject from the research, if such action appears in the subject's best interest.

Voluntariness. An agreement to participate in research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence. Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable.

Unjustifiable pressures usually occur when persons in positions of authority or commanding influence -- especially where possible sanctions are involved -- urge a course of action for a subject. A continuum of

such influencing factors exists, however, and it is impossible to state precisely where justifiable persuasion ends and undue influence begins. But undue influence would include actions such as manipulating a person's choice through the controlling influence of a close relative and threatening to withdraw health services to which an individual would otherwise be entitled.

2. Assessment of Risks and Benefits. —

The assessment of risks and benefits requires a careful arrayal of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research. For the investigator, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate.

The Nature and Scope of Risks and Benefits. The requirement that research be justified on the basis of a favorable risk/benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons. The term "risk" refers to a possibility that harm may occur. However, when expressions such as "small risk" or "high risk" are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm.

The term "benefit" is used in the research context to refer to something of positive value related to health or welfare. Unlike, "risk," "benefit" is not a term that expresses probabilities. Risk is properly contrasted to probability of benefits, and benefits are properly contrasted with harms rather than risks of harm. Accordingly, so-called risk/benefit assessments are concerned with the probabilities and magnitudes of possible harm and anticipated benefits. Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked.

Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society). Previous codes and Federal regulations have required that risks to subjects be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society in the form of knowledge to be gained from the research. In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight. On the other hand, interests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. Beneficence thus requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research.

The Systematic Assessment of Risks and Benefits. It is commonly said that benefits and risks must be "balanced" and shown to be "in a favorable ratio." The metaphorical character of these terms draws attention to the difficulty of making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research, and to consider alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and investigators less subject to misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible. The method of ascertaining risks should be explicit, especially where there is no alternative to the use of such vague categories as small or slight risk. It should also be determined whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.

Finally, assessment of the justifiability of research should reflect at least the following considerations: **(i)**Brutal or inhumane treatment of human subjects is never morally justified. **(ii)** Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures. **(iii)** When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject -- or, in some rare cases, to the manifest voluntariness of the participation). **(iv)** When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits. **(v)** Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

3. Selection of Subjects. —

Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.

Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favor or select only "undesirable" persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (e.g., adults before children) and that some classes of potential subjects (e.g., the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.

Injustice may appear in the selection of subjects, even if individual subjects are selected fairly by investigators and treated fairly in the course of research. Thus injustice arises from social, racial, sexual and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research subjects fairly, and even if IRBs are taking care to assure that subjects are selected fairly within a particular institution, unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions or investigators may not be able to resolve a problem that is pervasive in their social setting, they can consider distributive justice in selecting research subjects.

Some populations, especially institutionalized ones, are already burdened in many ways by their infirmities and environments. When research is proposed that involves risks and does not include a therapeutic component, other less burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions of the class involved. Also, even though public funds for research may often flow in the same directions as public funds for health care, it seems unfair that populations dependent on public health care constitute a pool of preferred research subjects if more advantaged populations are likely to be the recipients of the benefits.

One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

[1] Since 1945, various codes for the proper and responsible conduct of human experimentation in medical research have been adopted by different organizations. The best known of these codes are the Nuremberg Code of 1947, the Helsinki Declaration of 1964 (revised in 1975), and the 1971 Guidelines (codified into Federal Regulations in 1974) issued by the U.S. Department of Health, Education, and Welfare Codes for the conduct of social and behavioral research have also been adopted, the best known being that of the American Psychological Association, published in 1973.

[2] Although practice usually involves interventions designed solely to enhance the well-being of a particular individual, interventions are sometimes applied to one individual for the enhancement of the well-being of another (e.g., blood donation, skin grafts, organ transplants) or an intervention may have the dual purpose of enhancing the well-being of a particular individual, and, at the same time, providing some benefit to others (e.g., vaccination, which protects both the person who is vaccinated and society generally). The fact that some forms of practice have elements other than immediate benefit to the individual receiving an intervention, however, should not confuse the general distinction between research and practice. Even when a procedure applied in practice may benefit some other person, it remains an intervention designed to enhance the well-being of a particular individual or groups of individuals; thus, it is practice and need not be reviewed as research.

[3] Because the problems related to social experimentation may differ substantially from those of biomedical and behavioral research, the Commission specifically declines to make any policy determination regarding such research at this time. Rather, the Commission believes that the problem ought to be addressed by one of its successor bodies.

REVISION HISTORY

Revision Number	Description of Changes	Approvals	Date
N/A	Initial Release of the PPMH IRB Handbook	PPMH IRB Committee	4-27-2022
1	Corrected grammatical errors in document.		