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**HRPP STANDARD OPERATING PROCEDURE/POLICY APPROVAL &
IMPLEMENTATION**

OFFICE OF HUMAN SUBJECTS RESEARCH PROTECTIONS

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**SOP Title: NIH PUBLIC HEALTH EMERGENCY RESEARCH REVIEW BOARD
(PHERRB)**

**Distribution: Scientific Directors; Clinical Directors; Clinical Investigators, IRB
Chairs, IRB Administrators, Protocol Navigators**

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**SOP 28. NIH PUBLIC HEALTH EMERGENCY RESEARCH REVIEW BOARD
(PHERRB)**

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SOP 28. NIH PUBLIC HEALTH EMERGENCY RESEARCH REVIEW BOARD (PHERRB)

28.1 PURPOSE

This SOP describes NIH policies and responsibilities of the lead and site principal investigators (PIs), NIH Institutional Review Boards (IRBs) serving in the capacity of the Public Health Emergency Review Board or “PHERRB”, NIH Office of Human Subjects Research Protections (OHSRP), and relying institutions, referred to as “Institutions,” when one of the NIH IRBs is the IRB of record for multisite public health emergency research (PHER) protocols that require IRB review and, on a case-by-case basis, single site PHER protocols.

28.2 BACKGROUND

The Public Health Emergency Research Review Board (PHERRB) was established as a central IRB to provide IRB review of multi-site PHER protocols that are: (1) conducted, supported, or regulated by DHHS and (2) subject to the Common Rule (45 CFR 46) and/or FDA human subjects protections and IRB regulations (21 CFR parts 50 and 56), as applicable (Appendix 1). The PHERRB policies and pre-IRB activities are administered by OHSRP. Exempt research is not subject to PHERRB review.

28.3 POLICY

The PHERRB will provide efficient and rigorous IRB review of eligible and appropriate PHER protocols involving human subjects, e.g., biomedical and behavioral research, health services research, and public health research. (Eligibility criteria are discussed more fully in 28.6). The PHERRB, as a public resource, is available both to NIH intramural investigators and to investigators from outside institutions that agree to rely upon the PHERRB for such review.

PHERRB review and oversight complies with the regulatory requirements set forth in 45 CFR 46 (Appendix 1.B) and/or 21 CFR parts 50 and 56 (Appendix 1.C), as applicable, for approving and overseeing PHER conducted by NIH investigators and/or when other institutions rely upon the PHERRB for such review. The PHERRB may review research conducted under an investigational new drug

application (IND) (21 CFR 312) (Appendix 1.4) or an investigational device exemption application (IDE) (21 CFR 812) (Appendix 1.5).

The NIH Director has delegated to the Deputy Director for Intramural Research (DDIR) the authority to provide guidance on whether PHER research proposed for review by the PHERRB is appropriate for such review. Any of the NIH IRBs may serve as the PHERRB.

For non-NIH investigators, the PHERRB will review research under an executed NIH IRB Reliance (Authorization) Agreement. The PHERRB will act as the IRB of record in accord with this policy and other applicable NIH SOPs, like NIH SOPs 20 - NIH HRPP Requirements for Collaborative Research, SOP 20A - Obtaining a Reliance (Authorization) Agreement at the NIH, and, as applicable, SOP 20B - NIH IRB Responsibilities When Reviewing Local Context Considerations for Offsite Research (Appendix 1.D). PHERRB review will meet the human subject protection requirements of the relying institution's Office for Human Research Protections (OHRP)-approved federalwide assurance (FWA).

NIH investigators must follow NIH policy for human subjects protection as outlined, e.g., in the NIH HRPP SOPs (see Appendix 1- List of Links). Non-NIH investigators and institutions will follow 45 CFR 46 and, as applicable, 21 CFR parts 50 and 56, this SOP, the executed reliance agreement, and local institutional policies, law and regulations, as applicable. The NIH Institutional Official has the authority to waive or modify NIH HRPP policy requirements in response to a public health emergency.

28.4 DEFINITIONS

For purposes of this SOP, the following definitions apply:

- A. IRB Authorization Agreement (IAA)/Reliance Agreement:** An agreement between NIH and an institution engaged in human subjects research that assigns regulatory responsibilities for IRB review to the NIH. The terms "authorization agreement" and "reliance agreement" are used interchangeably in this SOP. At NIH, the preferred term is "reliance agreement."

- B. Centralized IRB Review Process:** A centralized IRB review process that involves an agreement in which institutions engaged in multi-site, cooperative research rely in whole or in part on the review of a single,

designated IRB that may or may not be affiliated with the research site(s). This “central IRB” may also be called the lead IRB.

- C. Cooperative Research:** Research in which more than one institution is engaged in human subjects research. See, e.g., 45 CFR 46.114.
- D. Coordinating Center or Site:** A Coordinating Center is the entity that is responsible, in multi-site studies, for coordination, including, as applicable, for overall planning, document collection, monitoring and communication among all sites participating in a multi-site research project. A Coordinating Center may also be responsible for data management and analysis and may be designated either by a funder, sponsor or by mutual agreement of the participating sites.
- E. Data Safety and Monitoring Board (DSMB)** (also known as a Data and Safety Monitoring Committee [DSMC] or Data Monitoring Committee [DMC]): A formal committee made up of experts, who are not the trial organizers or investigators, which reviews, on a regular basis, accumulating data from one or more ongoing clinical trials.
- F. Human Subject:** A living individual about whom an investigator (whether professional or student) conducting research obtains (a) data through intervention or interaction with the individual, or (b) identifiable private information (45 CFR 46.102(f)).
- G. Research:** a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge (46 CFR 46.102(d)).
- H. Institutional Official:** The institutional official (IO) is a signatory on the federalwide assurance (FWA) filed with the Office for Human Research Protections (OHRP). The IO has the authority to represent the institution named in the FWA.
- I. Lead Principal Investigator (Lead PI):** Investigator with overall responsibility for overseeing a multi-site study, submitting the protocol to the PHERRB and ensuring all engaged sites have the most current version of the IRB-approved protocol. The Lead PI can also be a Site PI.
- J. Local Context:** In this SOP, this term refers to unique legal requirements,

cultural or religious values, or other site-specific variables that exist at a site where subjects are enrolled in research protocols.

- K. Multi-Site protocol** (multi-site research): Multi-site research/protocols refer to projects that will be conducted at more than one location. Usually a multi-site study involves conduct of an entire protocol carried out at more than one medical institution or site. Sites may also include schools, nursing homes, community rehabilitation facilities, private practices, individual homes, etc.
- L. NIH Investigator:** Investigator, on a protocol, who is employed by NIH.
- M. Non-compliance:** The failure to comply with applicable NIH HRPP policies, PHERRB stipulations or directives, or other regulatory requirements for the protection of human research subjects (see Revised! SOP 16 - Reporting Requirements for Unanticipated Problems, Adverse Events and Protocol Deviations). Non-compliance may be further characterized as:
1. **Serious non-compliance:** Non-compliance that:
 - a. Increases risks, or causes harm, to participants.
 - b. Decreases potential benefits to participants.
 - c. Compromises the integrity of the NIH HRPP.
 2. **Continuing non-compliance:** Non-compliance that is recurring. An example may be a pattern of non-compliance that suggests a likelihood that, absent an intervention, non-compliance will continue. Continuing non-compliance could also include a failure to respond to PHERRB requests to resolve previous allegations of non-compliance.
- N. Non-NIH Investigator:** Investigator, on a protocol, who is not employed by the NIH.
- O. Protocol Deviation (PD):** Any change, divergence, or departure from the IRB-approved research protocol. The impact of a PD is characterized by designation as serious or not serious. The following protocol deviations must be reported to the IRB: 1) Those that occur because a member of the research team deviates from the protocol; 2) Those that are identified before they occur, but cannot be prevented (e.g., when a subject alerts the research team that inclement weather will prevent the subject from attending a scheduled protocol visit); and 3) Those that are discovered after they occur. This term also includes the reporting of deviations from an investigational

plan performed to eliminate immediate apparent hazards to the subject as required in FDA regulated research.

- P. Public Health Emergency Research (PHER):** Research protocols that are designed to address public health emergencies, including but not limited to preparing for, mitigating, or otherwise responding to public health emergencies that are naturally occurring, accidental or deliberate; are caused by biological, chemical, or radiological agents (e.g., infectious disease outbreaks, natural disasters, or bioterrorist events); or are the results of socioeconomic crises. PHER research may include research conducted under an investigational new drug application (IND) or an investigational device exemption application (IDE).
- Q. Site Principal Investigator (Site PI):** A single investigator with responsibility for overseeing all aspects of the study at a given site and who coordinates communication with the Lead PI.
- R. Unanticipated Problem (UP):** Any incident, experience, or outcome that meets **all** of the following criteria:
1. **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;
 2. **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
 3. 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.

Expected Adverse Events may become UPs if they occur at a greater frequency or severity than was previously expected (see Appendix 1, NIH HRPP SOP 16.)

- S. Unanticipated Adverse Device Effect (UADE):** Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

28.5 PROCESS FOR REQUESTING PHERRB REVIEW

- A. The Lead PI will submit the Application for PHERRB Review to OHSRP (Attachment 1). The PI should obtain concurrence from his or her local site's Institutional Official for conduct of the proposed research prior to submitting an Application for PHERRB Review.
- B. OHSRP reviews the Application for PHERRB Review and makes a recommendation to the NIH Director, or his or her designee, regarding eligibility and/or appropriateness of a protocol for PHERRB review.
- C. OHSRP will notify the Lead PI regarding acceptance of the protocol for PHERRB review.
- D. For accepted protocols, engaged institutions must apply for and enter into reliance agreements as described in section 28.7.
- E. The Lead PI must submit documentation for initial review by the PHERRB, as described in section 28.8.C.

28.6 PROTOCOL ELIGIBILITY REQUIREMENTS FOR PHERRB REVIEW

- A. A protocol must meet the following criteria to be eligible for PHERRB review:
 - 1. Generally, it must be conducted, supported, or regulated by DHHS; however protocols also conducted, supported or regulated by other, non-DHHS agencies or sponsors may be approved for PHERRB review on a case by case basis;
 - 2. It must be PHER;

3. It must be a multi-site study or otherwise require multiple IRB review. (single site studies may be approved for PHERRB review on a case-by-case basis);
4. It must be subject to the Common Rule (45 CFR 46) and, if applicable, FDA human subjects protections and IRB regulations (e.g., 21 CFR parts 50, 56, 312 and 812). Regulations of other, non-DHHS agencies may apply on a case by case basis, if a protocol is conducted, supported, or regulated by a non-DHHS agency is approved; and
5. It must be subject to IRB review pursuant to 45 CFR 46 and, if applicable, 21 CFR 56. The PHERRB will not review “exempt” research as defined in those regulations.

28.7 RELIANCE AGREEMENTS BETWEEN THE NIH AND RELYING INSTITUTION(S)

- A. If OHSRP finds that a protocol is eligible and appropriate for PHERRB review, a reliance agreement between NIH and the Lead PI’s institution(s) as well as other engaged study site institutions, consistent with NIH HRPP SOP 20A, as applicable, must be obtained before the protocol may be reviewed by the PHERRB. The NIH will only enter into a reliance agreement with an institution that has a valid Federalwide Assurance (FWA) approved by the OHRP. For institutions (or individuals) engaged in PHER research that do not have an FWA, NIH or another FWA-holding entity may consider extending its FWA (see NIH HRPP SOP 20D). The relying institution(s) will have responsibilities as set forth in the reliance agreement and, in addition, may have other responsibilities to protect human subjects under its own policies and/or applicable state or local law.
- B. The Lead PI, Site PI, or other representative from each institution seeking a reliance must complete the “Initial Application for Reliance Agreement” which can be found on the OHSRP website in NIH HRPP SOP 20A (Appendix 1.A). A copy of the proposed protocol must be submitted when requesting a reliance agreement.

- C. The NIH OHSRP will evaluate the “Initial Application for Reliance Agreement” following the criteria set forth in NIH HRPP SOP 20A.
- D. OHSRP will work with the applicant(s) to facilitate the process using a Reliance Agreement template approved by NIH Office of General Counsel (OGC). A request for changes to the approved NIH template requires clearance by NIH OGC and may result in delays.

28.8 RESPONSIBILITIES OF THE LEAD PRINCIPAL INVESTIGATOR (PI)

A. Submission of application for PHERRB Review.

B. Scientific Review: The Lead PI is responsible for obtaining scientific review and approval of the protocol before the Lead PI submits documentation to the PHERRB for initial review. For example, scientific review and approval by a federal funder or Institution(s) generally will be sufficient. If additional questions regarding scientific review of the protocol arise during the PHERRB review, they must be addressed by on a case-by-case basis.

C. Submission of Documentation for Initial Review:

1. **Required Documentation.** The following documents must be submitted to the PHERRB for initial review:
 - a. Report of scientific review (see 28.8.B)
 - b. Initial protocol application (available via the NIH IRB electronic submission system)
 - c. Protocol document (containing content described in Attachment 2)
 - d. Proposed consent and/or assent form(s) (see 28.8.D)
 - e. Initial Review Local Context Worksheet (see Attachment 3)
 - f. A statement of whether the research requires an IND or IDE and supporting FDA IND/IDE documentation, as applicable (see 28.8.E)
 - g. Ancillary required reviews as applicable (see 28.9.G)
 - h. COI certifications and other COI documentation, as applicable (see 28.9.D and Appendix 3)

Other supporting documents can be submitted at this time.

2. **Required Elements of the Protocol:** The Lead PI may submit the protocol utilizing protocol templates from his or her Institution as long as the information contained in the protocol is sufficient to meet the criteria for approval in 45 CFR part 46.111 and, if applicable, FDA requirements (21 CFR parts 50, 56, 312 and/or 812) as applicable. The protocol must address the topics listed in Attachment 2 “Required Elements of a PHER Protocol”.
3. **Submission to the PHERRB:** The Lead PI will use the NIH protocol application(s), available via the NIH IRB electronic submission system, to submit the documents listed in 28.8.C.1, to the PHERRB.

D. Informed Consent

1. The Lead PI should submit an informed consent form as part of the protocol document submitted under section 28.8.C.1. The informed consent document must include the required elements of informed consent under 45 CFR 46.116 and, as applicable, FDA regulations (21 CFR parts 50, 54, 56, 312 or 812), unless requesting a waiver or alteration of informed consent, in compliance with the Common Rule and, as applicable, FDA regulations (21 CFR 50). All consent documents must adhere to NIH policy that such documents be understandable to potential research participants with no more than an 8th grade reading level. Non-NIH investigators may use their Institution’s informed consent template, if available. Note that the PHERRB cannot review research for compliance with Institutional policy or Institution’s state or local regulations.
2. For research that is subject to FDA regulations (e.g., 21 CFR parts 50, 54, 56, 312 or 812), the informed consent process, or a waiver of the informed consent should meet any applicable requirements (e.g., criteria under 21 CFR 50.24 for emergency research exception from informed consent requirements).
3. OHSRP can provide examples of informed consent form language to the Lead PI to assist with developing a form that meets the required elements of informed consent under 45 CFR 46.116

E. Research Regulated by the Food and Drug Administration

If the research is FDA-regulated, the following requirements apply:

1. Investigators and relying Institutions will comply with all applicable FDA requirements.
2. At the time of submission of documentation for initial protocol review by the PHERRB:
 - a. The Lead PI must inform the PHERRB whether the research requires an IND or IDE (for NIH investigators, see NIH HRPP SOP 15A or NIH HRPP SOP 15B, respectively);
 - b. If the research involves (a) investigational drugs, biologics or devices, or (b) the use of commercially available products for an off-label use, and there is no IND or IDE, the Lead PI must provide a rationale for why an IND or IDE is not required;
 - c. If an IND or IDE is required, the Lead PI must provide:
 - i. the IND/IDE number;
 - ii. written communication from the FDA indicating assignment of the IND or IDE number;
 - iii. Investigator's Brochure (IB) (or alternative communication), if available; and
 - iv. existing reports of prior investigations, or the package insert, as applicable.
3. If an IND/IDE is required by the FDA, the protocol will may not begin until a valid IND/IDE is in effect. The PHERRB will seek the opinion of the FDA, if necessary, to clarify whether a study involving investigational drugs or devices requires an IND/IDE.

F. Reporting Events at the Time of Continuing PHERRB Review: At the continuing review (CR), the Lead PI will provide the PHERRB with an aggregated summary of:

1. All UPs previously reported in real time (see Section 28.9 I-K) .

2. All PDs previously reported in real time (except anticipated PDs granted a waiver of reporting by the IRB)
3. All UADEs
4. All AEs (except expected AEs and deaths granted a waiver of reporting by the IRB); and
5. All research-related subject complaints

If, while preparing the CR report, the Lead PI identifies a greater frequency or level of severity of expected AEs than was previously expected and the aggregate information qualifies as a UP, the Lead PI must also report these AEs as UPs.

The Lead PI and the PHERRB must determine whether the reportable event requires changes in the protocol or consent and whether other actions are needed to protect the safety, welfare, or rights of study participants or others.

28.9 RESPONSIBILITIES OF ALL SITE PRINCIPAL INVESTIGATORS

Each Site PI must comply with the policies of his or her Institution, including, but not limited to: records management, privacy laws (item C below), conflict of interest (COI) (item D below), training requirements (item E below), and protocol monitoring and audits.

A. Regulatory Requirements

Site PIs are responsible for ensuring that their investigators and research staff follow the Common Rule and applicable FDA regulations (21 parts 50, 54, 56, 312 and 812).

B. Compliance with PHERRB Decisions

The Lead PI and Site PIs must accept the decisions and requirements of the PHERRB and comply with the terms of the NIH Reliance Agreement, as applicable.

C. Privacy and Confidentiality

Site PIs are responsible for ensuring that their investigators and research staff follow the privacy and confidentiality laws, regulations, and policies applicable to the research site, e.g. Institutions may be required to comply with the HIPAA Privacy Rule or the Privacy Act of 1974 (see Appendix 1.E) and other regulations.

D. Conflict of Interest

1. Non-NIH investigators and research staff must follow the conflict of interest (COI) clearance requirements of their Institution. If their Institution does not have COI clearance requirements, then they must follow the “NIH Guide to Avoiding Financial and Non-Financial Conflicts or Perceived Conflicts of Interest in Human Subjects Research at NIH” (see Appendix 3) as outlined in 28.10.A. The Lead PI will provide the PHERRB with documentation describing: each institution’s conflict of interest review process at the time of the initial protocol submission and with documentation of the COI review, for all covered investigators on the protocol, indicating whether there are any unmitigated or existing conflicts.
2. NIH investigators are responsible for ensuring that their research staff follows the applicable requirements of NIH HRPP SOP 21, “Conflict of Interest Requirements for Researchers and Research Staff.”

E. Training Requirements

1. Non-NIH Site PIs are responsible for ensuring that their investigators and research staff follow the human subject protection training requirements of the Site PI’s Institution. The Site PI will provide the PHERRB with his or her Institution’s training requirements and documentation that the Site PI has met these requirements.
2. If investigators do not have required HRPP training, OHSRP will determine what training should be completed.
3. NIH investigators and research staff will follow the training requirements described in NIH HRPP SOP 25.

- F. Subject Complaints:** Research subjects may bring concerns regarding their participation in research to the attention of the Site PI or other institutional representatives in a manner consistent with the policy of the research site.
- G. Local Research Context:** The Lead PI in collaboration with the Site PIs should submit an Initial Review Local Context Worksheet (Attachment 3) for each site to the PHERRB at the time of initial review, and should submit the Continuing Review Local Context Worksheet (Attachment 4) at the time of continuing review. This information shall include specific requirements of state and local laws, regulations, policies, standards or other factors applicable to the site that would affect the Institution's conduct of the PHER study. Institutionally required template, including any "boilerplate," language should be submitted with the local context worksheet or identified as part of the Institution's consent template, as appropriate.
- H. Ancillary Reviews:** If there are responsibilities other than those under 45 CFR 46 and/or 21 CFR 50 and 56, PHERRB review will not preempt or fulfill those responsibilities. The Site PI(s) must ensure that other required committee reviews (e.g., radiation safety, pharmacy, etc.) are completed by the Site PI's Institution. The Lead PI will provide the PHERRB with any results of such reviews that would affect its conduct of the study and ability to satisfy the applicable requirements for human subjects protection, e.g., IRB conditions or 45 CFR 46.
- I. Reporting Unanticipated Problems (UPs), Adverse Events (AEs), Protocol Deviations (PDs) and Non-compliance to the PHERRB**
1. NIH PIs are responsible for reporting possible UPs, AEs, PDs and non-compliance consistent with NIH HRPP SOPs 16, "Reporting Requirements for Unanticipated Problems, Adverse Events and Protocol Deviations" and 16A, "Allegations of Non-compliance with Requirements of the NIH Human Research Protection Program (HRPP)."
 2. Non-NIH Site PIs are responsible for reporting possible UPs, AEs, PDs and non-compliance to the PHERRB and Institutional leadership, and to the Lead PI, consistent with the terms of the authorization agreement and this SOP.

J. Method of Events Reporting: The Lead PI must report UPs, AEs, PDs and non-compliance to the PHERRB using the appropriate electronic IRB reporting system. If the PI is unable to access the appropriate IRB reporting system, the PI may use the NIH Problem Report Form. The PI may elect also to report serious unanticipated problems, protocol deviations and serious or continuing non-compliance to the PHERRB Chair/designee in person or by phone or e-mail. However, such reporting is in addition to reporting using the appropriate electronic IRB reporting system or NIH Problem Report Form.

K. Timing of Events Reporting

1. Serious Events: The Lead PI must report possible Serious UPs, Serious PDs, and UADEs to the PHERRB as soon as possible but not more than 7 days after the Lead PI first learns of the event.
 - a. FDA-regulated research: report consistent with applicable FDA and Sponsor requirements (e.g., as described in SOPs 15, 15A and 15B).
 - b. For device research, the Lead PI must report to the PHERRB any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency as soon as possible, but no later than 5 working days after the emergency occurred.
2. Not Serious Events: The Lead PI must report all UPs and PDs that are not serious to the PHERRB not more than 14 days after the Lead PI learns of the event.
 - a. FDA-regulated research: report consistent with applicable FDA and Sponsor requirements (e.g., as described in SOPs 15, 15A and 15B).
3. Adverse events that are not UPs must be documented and submitted by the Lead PI at the time of PHERRB continuing review.
 - a. FDA-regulated research: report consistent with applicable FDA and Sponsor requirements (e.g., as described in see SOPs 15, 15A and 15B).

28.10 RESPONSIBILITIES OF THE RELYING INSTITUTION

In general, Institutions must comply with the executed Reliance Agreement with NIH and its institutional HRPP policies. The following provisions are for clarification purposes and are not meant to limit in any way the Institution's responsibilities under the Reliance Agreement or its HRPP policies.

A. Conflict of Interest

1. If the Institution has a written administrative process to identify and manage, reduce, or eliminate conflicting financial interests with respect to research projects ("COI policy"), it must perform its own investigator COI analysis under its relevant policies. The Lead PI must certify compliance as part of the information provided to the PHERRB at the time of the initial protocol submission.
2. Only if the Institution does not have a COI policy, the Institution must abide by the "A Guide to Avoiding Financial and Non-Financial Conflicts or Perceived Conflicts of Interest in Human Subjects Research at NIH" (see Appendix 3) (NIH Guide) and will provide the NIH Guide to PHER investigators and research staff. The Lead PI must certify compliance as part of the information provided to the PHERRB at the time of initial submission of the protocol (see Section 28.8. C).

B. Ancillary Committee Review

The Institution will conduct any applicable ancillary reviews (such as radiation safety, pharmacy, etc.) required by its policies.

C. HIPAA, Privacy and Confidentiality

The Institution will be independently responsible for overseeing compliance with privacy and confidentiality requirements applicable to it that do not involve the PHERB and its obligations under 45 CFR 46 and/or, as applicable, FDA regulatory requirements. These include, for example and if applicable, compliance with the HIPAA Privacy Rule (45 CFR 160, 164), and state laws affecting confidentiality of individual medical records. For more information see Appendix 1.

D. Conduct of Research

Although PHER sites will rely on the PHERRB for IRB oversight, the Institution continues to have responsibility under the Common Rule for any duties not undertaken by PHERRB, as well as state and local laws, and, as applicable, FDA requirements pertaining to the conduct of the research and the safety of the research subjects.

E. ClinicalTrials.gov Registration of the Protocol

The Lead PI's Institution will assure that any requirements for protocol registration in ClinicalTrials.gov, a publicly accessible database operated by the National Library of Medicine (NLM), are met (Appendix 1.F).

28.11 RESPONSIBILITIES OF THE PUBLIC HEALTH EMERGENCY RESEARCH REVIEW BOARD (PHERRB)

The PHERRB is responsible for serving as the IRB of record for accepted PHER protocols, and the PHERRB will begin the review process as soon as possible after a reliance agreement has been executed between NIH and the relying Institution.

PHERRB review will meet the human subject protection requirements of the relying Institution's OHRP-approved federalwide assurance (FWA), and it will be conducted consistent with 45 CFR 46 and/or, as applicable, 21 CFR 50 and 56, the PHERRB Terms of Reference (Appendix 2), and, as applicable, NIH HRPP SOPs regarding IRB review. PHERRB responsibilities include, but are not limited to, the following:

A. Schedule of Meetings

The PHERRB will meet, as needed, at the request of the NIH Director or designee.

B. Use of Consultants

Consistent with 45 CFR 46.107(f) and 21 CFR 56.107(f), on an as-needed basis, the PHERRB may invite individuals with experience in special areas as non-voting consultants to assist in the review of studies that require expertise beyond or in addition to that available on the PHERRB.

C. Review of Local Context Concerns

The designated PHERRB will review the protocol according to NIH policies on local context reviews, as described in SOP 20B, using the Initial Review Local Context Worksheet (Attachment 3). At time of CR the PHERRB will also review the Continuing Review Local Context Worksheet (see Attachment 4).

D. Research Involving Vulnerable Subjects

The review of research involving vulnerable human subjects will follow the requirement of the Common Rule, NIH HRPP SOPs 14A-F, and, as applicable, 21 CFR part 50.

E. Adverse Events (AEs), Unanticipated Problems (UPs), Protocol Deviations (PD's), Non-compliance and Subject Complaints

The PHERRB must review reports of unanticipated problems, protocol deviations and serious or continuing non-compliance when the Lead PI or other individual/entity reports an experience or outcome (See 28.8.F, 28.9.H). Non-UP AEs and subject complaints of which the PHERRB is aware will be reviewed at the time of the continuing review.

28.12 NIH OFFICE OF HUMAN SUBJECTS RESEARCH PROTECTIONS (OHSRP) RESPONSIBILITIES

OHSRP responsibilities include the following:

- A. Determining whether reporting of the following to the Office for Human Research Protections (OHRP) or FDA is necessary, and, if so, making such reports regarding:
 - 1. Events determined by the PHERRB to constitute unanticipated problems or serious and/or continuing noncompliance;
 - 2. PHERRB action to suspend or terminate a PHER protocol.

- B. Reviewing Institutional boilerplate language, such as consent templates, of PHER sites for any institutional policy or language conflict with NIH HRPP SOPs or boilerplate language.
- C. Reviewing the Application for PHERRB Review.
- D. Assuring the appropriate execution of an NIH IRB Reliance Agreement with outside institutions, consistent with SOP 20A. The agreement will be signed by the NIH Signatory official or his or her designee.
- E. Determining what training should be taken by investigators who do not have adequate institutional training requirements.
- F. Preparing annual PHERRB report to the NIH Director.

28.13 LIST OF APPENDICES

Appendix 1- List of Links

Appendix 2 - PHERRB Terms of Reference

Appendix 3 - NIH Guide to Avoiding Financial and Non-Financial Conflicts or Perceived Conflicts of Interest in Human Subjects Research at NIH

28.14 LIST OF ATTACHMENTS

Attachment 1: Application for PHERRB Review

Attachment 2: Required Elements of a PHER Protocol

Attachment 3: Initial Review Local Context Worksheet

Attachment 4: Continuing Review Local Context Worksheet

APPENDIX 1- LIST OF LINKS

- A. OHSRP Website with NIH HRPP SOPs and Link to PHERRB Materials: <http://ohsr.od.nih.gov>
- B. The Common Rule (45 CFR 46): <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>
- C. FDA regulations (Title 21):
 - 1. 21 CFR Part 50: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?CFRPart=50>
 - 2. 21 CFR Part 54: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?CFRPart=54>
 - 3. 21 CFR Part 56: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?CFRPart=56>
 - 4. 21 CFR Part 312: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?CFRPart=312>
 - 5. 21 CFR Part 812: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?CFRPart=812>
 - 6. IND Toolbox for Investigator Initiated INDs including Emergency INDs: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugs/INDApplication/ucm343349.htm>
- D. The Privacy Act of 1974, 5 U.S.C. § 552a: <http://www.hhs.gov/foia/privacy/index.html>
- E. Clinical trial registration information www.clinicaltrials.gov.

APPENDIX 2 – PHERRB TERMS OF REFERENCE

PUBLIC HEALTH EMERGENCY RESEARCH REVIEW BOARD (PHERRB)

Terms of Reference, October 2012

Purpose and Scope

The Public Health Emergency Research Review Board (PHERRB) is established under the auspices of the National Institutes of Health (NIH) as a network of NIH Institute and Center (IC) Institutional Review Boards (IRBs) to carry out ethical review of research protocols that are designed to address public health emergencies and that are conducted, supported, or regulated by the U.S. Department of Health and Human Services (HHS) and subject to 45 CFR 46 and/or 21 CFR 50 and 56. Through a dedicated review of human subjects protections for research protocols that address public health emergencies, the PHERRB network will provide a critical national service by helping to assure that studies carried out across the country are rigorously and expeditiously reviewed to enable the ethical conduct of essential research in the context of these emergencies. The specific IRB within the network that will carry out the review for a particular protocol(s), which will depend on the nature of the study, will be designated as the IRB of Record under NIH's assurance from the Office for Human Research Protections (OHRP).

In serving to review human subjects research protocols that arise in connection with public health emergencies the PHERRB's jurisdiction includes, but is not limited to, protocols to prepare for, mitigate, or otherwise respond to emergencies that are naturally occurring, accidental or deliberate; are caused by biological, chemical, or radiological agents (e.g., infectious disease outbreaks, natural disasters, or bioterrorist events); or are the results of socioeconomic crises. Such research might include, for example, studies aimed at mitigating or otherwise responding to a public health emergency, exploring causes of a public health emergency, or addressing another public health need. Any type of research protocol involving human subjects, e.g., biomedical and behavioral research, health services research, and public health research, may be reviewed by the PHERRB. Such research includes research conducted under an investigational new drug application (IND) or an investigational device exemption application (IDE), including emergency and treatment INDs and IDEs, and IND or IDE research that is carried out concurrent with or in concert with Emergency Use Authorizations.

Functions

In compliance with 45 CFR 46 and/or 21 CFR 50 and 56, institutions and sponsors engaged in research involving human subjects that is conducted, supported, or regulated by HHS may rely on the NIH IC IRB serving as the PHERRB as the IRB of Record for its public health emergency research.

The NIH Director or designee will provide guidance on specific public health emergency research that is eligible for PHERRB review. In identifying protocols that are eligible for review by the PHERRB, the NIH Director, Assistant Secretary for Preparedness and Response (ASPR), Commissioner of Food and Drugs, and/or the Director of the Centers for Disease Control and Prevention (CDC) or their designees may be consulted.

Based on the criteria at 45 CFR 46.111 and 21 CFR 56.111, comparable regulations for research funded by other Federal agencies, if applicable, and all applicable subparts of these regulations, the NIH IC IRB serving as the PHERRB will either approve or disapprove a research proposal or it may require modification of the proposed research in order to grant approval.

The NIH IC IRB serving as the PHERRB will notify the principal investigator of the protocol, institution, and funding Agency (if any) of its decision to approve or disapprove any proposed research protocol or of modifications required to secure IRB approval of the research activity.

Structure and Membership

The PHERRB is a network of the 12 active IRBs of the NIH IRB system. These IRBs have discrete missions and research portfolios, and they regularly review research proposals submitted by intramural investigators working at the NIH. Each also has the role and responsibility of serving as the PHERRB when a public health emergency research protocol is submitted for PHERRB review. The selection of the individual IC IRB to perform the ethical review a particular protocol will depend on the focus of the research being proposed.

The membership of the PHERRB will be consistent with the requirements at 45 CFR 46.107 and 21 CFR 56.107. Non-voting ad hoc consultants will be added to the PHERRB as needed depending upon the subject matter being reviewed. Examples of additional expertise that may be needed on an ad hoc basis include the following:

- Knowledge of the expected cause of the public health emergency (e.g., a specific infectious agent, disease, or class of diseases; chemical or radiation-emitting agent; socioeconomic crisis) and of its effects on human health
- Knowledge of the populations, communities or regions under study in the proposed research; and/or
- Knowledge of the intervention or method of delivery proposed in the study

Procedures

PHERRB procedures, which are outlined in the Standard Operating Procedures of the NIH IRB System, comport with the requirements in 45 CFR 46 and 21 CFR 50 and 56 and will comply with institutional requirements as applicable.

Meetings

Meetings will be convened, as needed, at the request of the NIH Director or designee. All meetings will be conducted in compliance with procedures outlined at 45 CFR 46 and 21 CFR 56 and institutional requirements as applicable.

Support

The NIH will provide the organizational locus and management and support services for PHERRB.

Reports

The Executive Secretary will prepare an Annual Report for approval by the Chair of each NIH IC IRB that served as the PHERRB during the previous year each October 1 that will contain a summary of the proposals reviewed, actions taken, and any lessons learned. The consolidated Report will be submitted to the NIH Director as well as other HHS components.

Termination

The functions of the PHERRB can be dissolved at any time by the decision of the NIH Director after consultation with the Assistant Secretary for Health.

APPENDIX 3 - A GUIDE TO AVOIDING FINANCIAL AND NON-FINANCIAL CONFLICTS OR PERCEIVED CONFLICTS OF INTEREST IN CLINICAL RESEARCH AT NIH OCTOBER 2014

Avoiding financial and other conflicts of interests is important for NIH, where the trust and protection of research participants is vital to our mission to improve the public health. The number and complexity of laws and regulations in this area makes it difficult to know when there is a conflict or perceived conflict and what to do. This guide is intended to assist those engaged in clinical research and NIH IRB members in avoiding real or perceived financial and non-financial conflicts of interest.

I. What are potential conflicts of interest for those engaged in clinical research?

All NIH employees, including clinical researchers, when engaged in their NIH duties have an interest in advancing the public's health. For clinical researchers, these interests may include obtaining knowledge that will promote health and health care, and helping to ensure the safety and health of research participants. Employees often have other personal interests that could be affected by their NIH work such as a spouse's job, stock holdings and/or outside positions at universities and professional organizations. These outside interests are generally permissible, but in some circumstances they have the potential to compromise, or appear to compromise, the judgment of employees with respect to their NIH duties. When these outside interests have the potential to compromise the integrity of an employee's NIH work, a conflict of interests occurs between the employee's interest in his or her government work and his or her outside interests. Under the government rules, this conflict must be resolved before the employee can proceed to work on his or her NIH project.

This guide provides information to identify and prevent or mitigate financial and other conflicts, thereby helping to ensure both the integrity of our research and the safety of participants.

II. To whom does the guide apply?

The restrictions discussed in this guide are based on the laws that apply to NIH employees¹. These financial disclosure rules apply to those NIH employees, Special Government Employees (SGEs), and individuals at NIH under an Intergovernmental Personnel Act (IPA) agreement who have key decisional roles in protocols that may lead to financial benefit, termed “covered individuals”² and “covered protocols”³. These rules also apply to NIH employees who serve on NIH Institutional Review Boards (IRBs) and Data and Safety Monitoring Boards (DSMBs).

It is expected that non-NIH employees⁴ who are covered individuals or IRB or DSMB members⁵ will review this guide and adhere to the rules set out. Covered individuals who are not NIH employees should be mindful of real and potential conflicts and discuss such conflicts with the protocol’s PI and their home institution, as applicable. Non-federal employees must certify that they have received this guide and will comply with its tenets. Please note that the National Institutes of Health expects that all non-NIH investigators will comply with the ethics and conflict of interest policies and procedures set forth by their institution or employer.

III. Examples of investigator, covered individual, and IRB and DSMB member financial conflicts of interest

As noted below, some of these examples of financial conflicts of interest are prohibited by regulation for NIH employees. We list them, however, as guidance for non-NIH employee investigators, covered individuals, and IRB and DSMB members who are reviewing this guide. It should be noted that in addition to his or her own financial interests and outside interests, *an NIH employee’s financial interests also include the financial interests of others, such as his or her spouse, dependent children, or household members*. Examples of such interests are:

- Serving as a director, officer or other decision-maker for a commercial sponsor of clinical research (prohibited activity for NIH employees);
- Holding stock or stock options in a commercial sponsor of clinical research (unless below the applicable de minimis amount or held within a diversified, independently managed mutual fund);
- Receiving compensation for service as consultant or advisor to a commercial sponsor of clinical research (excluding expenses) (prohibited activity for NIH employees);
- Receiving honoraria from a commercial sponsor of clinical research (prohibited activity for NIH employees);
- Personally accepting payment from the clinical research sponsor for non-research travel or other gifts (for NIH employees, government receipt of in-kind, research-related travel is not included and other exceptions may apply);
- Obtaining royalties or being personally named as an inventor on patents (or invention reports) for the product(s) being evaluated in the clinical research or products that could benefit from the clinical research (special rules apply in this case when NIH holds the patent – see Section VII below);

- Receiving payments based on the research recruitment or outcomes (prohibited activity for NIH employees);
- Having other personal or outside relationships with the commercial sponsor of the clinical research (prohibited activity for NIH employees);
- Having financial interest above the applicable de minimis in companies with similar products known to the investigator to be competing with the product under study (prohibited activity for NIH employees); or
- Participating in an IRB or DSMB decision that has the potential to affect your spouse's employer (prohibited activity for NIH employees).

IV. Examples of non-financial real or apparent conflicts of interest for IRB and DSMB members

- Voting on a protocol when the member of the IRB is the protocol's Principal Investigator, Associate Investigator or study coordinator;
- Voting on a protocol when the member of the IRB or DSMB is or has a spouse, child, household member or any other individual with whom the protocol's Principal Investigator, Associate Investigator or study coordinator has the appearance of a conflict of interest; or
- Voting on a protocol when the protocol's Principal Investigator is the IRB member's supervisor (up the chain of command to the Clinical Director).

As noted in Section II - The National Institutes of Health expects that all non-NIH investigators are in compliance with their institutional/employer's conflict of interest policies.

CLEARANCE OF NIH EMPLOYEES ONLY – PERSONAL FINANCIAL HOLDINGS

V. NIH's system to assist in identifying and preventing personal financial conflicts for investigators in covered clinical research protocols

The Principal Investigator of a covered protocol is responsible for assuring that each covered individual receives a copy of this guide. The guide should be distributed to any new covered individual added to a protocol while the protocol is active. All NIH employees, and individuals who are not federal employees, who are covered individuals shall acknowledge receipt of this guide via a written or electronic statement. Certain NIH employees (those who are Principal Investigators (PIs), accountable investigators, medical advisory investigators, associate investigators (AIs), or other subinvestigators, such as Lead Associate Investigators) on covered protocols are required to disclose the value of all interests in Substantially Affected Organizations⁶ (SAOs) held or acquired personally or by their spouses or minor children. This is done by filing Form

717-1, Confidential Report of Financial Interests in Substantially Affected Organizations for Employees of the National Institutes of Health (available at <http://ethics.od.nih.gov>), and/or a *Confidential Financial Disclosure Report (Form OGE-450)*. Non-federal employees, and NIH employees who do not file an OGE-450 or 717-1 form will provide the PI with a Conflict of Interest (COI) Certification form.

a. New Protocols

For any covered protocol, at the earliest point possible, the PI is responsible for providing his or her IC Deputy Ethics Counselor (DEC) with a completed copy of the **“Clearance of NIH Investigator Personal Financial Holdings” (PFH Clearance)** (see Appendix 1), which lists all covered individuals. Alternatively, an electronic equivalent could be used to provide this information. If applicable, the PI also will provide copies of the signed Conflict of Interest (COI) Certification for Non-Federal Employees, or the Conflict of Interest (COI) Certification for NIH Employees Who Do Not File form 450 or 717-1.

For each protocol:

- 1) The DEC will verify that all covered individuals have submitted a form 450 or 717-1 or one of the two COI certification forms, if appropriate. The DEC will verify that the personal investment information on the form 450 or 717-1 is current (within 6 months) as of the date on the PFH Clearance. The IC DEC will then review file copies of the 450 or 717-1 forms that enumerate stock holdings in Substantially Affected Organizations (SAOs).
- 2) If SAO holdings are above the de minimis values, the DEC will provide the PI with an anonymous list of the covered individual’s holdings in SAOs as reported on these forms so the PI can determine if any pose a conflict of interest for the protocol in question. Any covered individual who has a potential conflict will be contacted by his or her DEC to determine how to resolve any actual or apparent conflict. The employee’s supervisor and/or the Clinical Director will be consulted as necessary if a conflict exists. The conflicts review will occur in parallel to the IRB submission process.

At the completion of the personal financial holdings review, the IC DEC will return a signed copy of the Protocol PFH Clearance to the PI. The PI will then note the date of DEC clearance on the *Protocol Application* and ensure that the Protocol PFH Clearance is included in the protocol packet.

The DEC clearance form will become part of the protocol packet forwarded to the IRB Chair for final approval. The IRB chair may not provide final approval by signing a protocol until the completed Protocol PFH Clearance is included in the protocol packet.

The PFH form may be submitted, reviewed and returned using electronic systems for protocol submission.

b. Continuing Review

A COI analysis will take place at the time of continuing review using the same process as described above. The Protocol PFH Clearance will be used for this process. For the conflicts analysis, the IC

DEC will evaluate the addition of new covered individuals, any changes related to the use of commercial products (as part of the scientific hypothesis) or any change to an IND/IDE.

c. Amendment

A COI analysis will take place for amendments involving the addition of covered individuals to a protocol, any changes related to the use of commercial products (as part of the scientific hypothesis), or any addition of an IND/IDE. The Protocol PFH Clearance will be used for this process following the procedure above. If just adding a new covered individual, only that individual needs to be cleared.

Although government-wide regulations allow NIH employees to hold de minimis amounts of publicly-traded stock without triggering conflict of interest restrictions, there may be other factors to consider with respect to stock ownership. If a publication should result from the protocol, most journals require the authors to disclose individual financial holdings within the text of the published paper. Such disclosures could raise at least the appearance of the conflict of interest. Thus, all investigators should consider these outside factors when making personal financial investments.

VI. IRB and DSMB Clearance for COI

- Before beginning protocol review activities, the Chair asks whether any member is aware of any real or apparent conflict of interest. The minutes will reflect which individual(s) has a real or apparent conflict of interest. No IRB or DSMB may have a member participate in the initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB or DSMB.
- When the Principal Investigator or Associate Investigator is the Institute Director, or Scientific Director, the protocol will be reviewed by an IRB not affiliated with that institute. The Deputy Director for Intramural Research may waive this requirement.
- When the Principal Investigator is the Clinical Director (CD) it shall be the prerogative of an IRB either to review such protocols or refer them to another Institute's IRB. IRBs reviewing protocols in which their CD is the PI must have a majority of voting members present at the meeting who are not employed by the CD's Institute, otherwise an alternative plan must have prior approval by the Clinical Center Director and the Deputy Director for Intramural Research.

VII. NIH Intellectual Property and Royalties

In some instances, NIH clinical research protocols will evaluate or potentially advance product(s) in which NIH (i.e., the government) owns patents or has received invention reports. In such cases:

- An NIH investigator may participate in the clinical trial, even if the investigator is listed on the patent or invention report and/or may receive royalty payments from the NIH for the product(s) being tested.

- When such an investigator participates in a trial, there will be full disclosure of the relationship to the IRB and to the research subjects (i.e., information should appear in the consent form) with review and approval by the IRB. This is to ensure the quality and integrity of the data collected.
- In the case of continuing review of current protocols where NIH has a new or amended intellectual property interest in the invention, the Principal Investigator should provide a new human subjects consent form or correspondence outlining the relationship, for review and approval by the IRB.

An independent entity or individual must review the integrity/accuracy of the results/quality of data to assure the safety of human subjects and to assess whether there is a change in the risk benefit ratio or introduction of possible bias.

ATTACHMENT 1: APPLICATION FOR PHERRB REVIEW

Date (DD/MM/YYYY):	
Name and Address of Institution:	
Lead Principal Investigator:	Work Address:
Work Phone:	
Work E-mail:	
Title of Protocol:	
List Study Co-investigators and key personnel, including any contractors engaged in the research:	
1.	
2.	
3.	
4.	
5.	
Do all investigators and key research personnel have current human subject protections training?	
Yes <input type="checkbox"/> No <input type="checkbox"/>	

PROJECT DESCRIPTION

List five keywords that describe your project:

- 1.
- 2.
- 3.
- 4.
- 5.

Has scientific review taken place for this protocol? Yes No

If yes, what institution was responsible for the scientific review and when did it occur?
Please attach documentation of scientific review.

Has funding been secured for this protocol? Yes No

If yes, what is the funding source(s) or sponsor?

What is your risk assessment of the entire protocol?

Minimal risk Minor increase over minimal risk Greater than minimal risk

Please list study sites where research will be performed:

When will the study commence?

Primary aims of study:

Secondary aims:

Briefly describe the scientific rationale for the study (500 words or less):

Briefly describe the proposed research design (750 words or less):

Will this Study use any FDA regulated drug/biologic or device?

Yes No

If yes, has an application for an IND/IDE been submitted to FDA? Yes No

If yes, provide any additional details if applicable, such as IND/IDE number.

List participating pharmaceutical, biologic or device manufacturing companies (if any):
Subject selection criteria: Inclusion Criteria - Exclusion Criteria -
Proposed number of subjects to be enrolled: Indicate if any of the following vulnerable populations will be included: <input type="checkbox"/> Children <input type="checkbox"/> Pregnant Women, Neonates, Human Fetuses <input type="checkbox"/> Cognitively Impaired <input type="checkbox"/> Prisoners
Please describe the informed consent process (500 words or less).
What other committee approvals will be required by your institution? (e.g., radiation safety, pharmacy)
Institutional Signatory Official (Name and Title) Work Address: Work Phone: Work E-mail:

Please attach the *curriculum vitae* of the PI and all co-investigators.

**Please e-mail the completed application and attachments
to PHERRB@mail.NIH.gov**

**Please call the NIH Office of Human Subjects Research Protections (OHSRP) with
any questions 301-402-3444**

ATTACHMENT 2: REQUIRED ELEMENTS OF A PHER PROTOCOL

Note: Text in italics is instructional.

TITLE

PRINCIPAL INVESTIGATOR

PRÉCIS

The purpose of the précis is to provide a short summary. For protocols with an NIH Lead PI, the précis is used to post this scientific summary on CT.gov. The précis is used by some institutes in the review of financial conflict of interest.

I. BACKGROUND INFORMATION, SCIENTIFIC RATIONALE AND SIGNIFICANCE

This section should be no more than 10 pages in length. References should be included but do not count toward the page limit.

A. Historical background

B. Previous pre-clinical or clinical studies leading up to, and supporting the proposed research (for example, include description of experimental drug or device if any)

C. Rationale and scientific basis for the proposed research, and potential benefits to patients and/or society

II. SPECIFIC AIMS (Research Objectives)

A. Objectives and/or hypotheses to be tested

State in bullet form the primary and secondary study objectives. Objectives should be tied to measurable endpoints described in subsequent sections of the protocol (e.g., statistical section, survival, response, surrogate markers) and all endpoints must be clearly defined.

1. Primary objective

The primary objective provides the major focus of the study and takes priority over other aspects of the study and drives statistical analyses.

2. Secondary objective(s) (if applicable)

Secondary objectives allow for investigation of contributory questions that, while scientifically important, do not have the same significance as the primary objective.

3. Exploratory objective(s) (if applicable)

III. STUDY DESIGN

A. Study design summary

Brief description of what study design has been selected

B. Study endpoints/outcome measures

Identify Primary and Secondary outcome measures

- *Outcome measures should be prioritized*
- *Generally, there should just be one primary variable with evidence that it will provide a clinically relevant, valid and reliable measure of the primary objective (e. g. lab procedure, safety measure)*
- *Secondary outcome measures should be included whether or not they add information about the primary objective or address secondary objectives. Discuss their importance and role in the analysis and interpretation of study results.*

IV. STUDY POPULATION

A. Description of study populations including any vulnerable subjects.

(For more information about vulnerable subjects in research see NIH HRPP SOP “14A – Research Involving Human Subjects.”)

- *Provide brief description of type of subject groups*
- *State accrual number for each group*
- *State target number of completers if applicable*

State if withdrawals/dropouts will be replaced

B. Rationale for subject selection

The protocol must include a rationale for research subject selection based on a review of gender/ethnic/race categories at risk for the disease/condition being studied; justify any exclusion based on considerations such as gender, race/ethnicity, age, pregnancy

C. Inclusion criteria

- *Do not list the same criterion under inclusion and exclusion (e. g. include age 18 and over, exclude age under 18)*
- *Describe co-enrollment guidelines for concurrent participation in other protocols (if applicable)*

D. Exclusion criteria

V. STUDY SCHEDULE AND METHODS

Describe all phases of the study, in chronological order when possible, including:

A. Study Overview

- *Summarize study design, number of visits, site location, and duration of visits and how long a person will be in the study*
- *State which visits are inpatient or outpatient*
- *Identify relationship of this study to other protocols (specify if subjects are required to participate in other protocol)*

B. Screening

- *Describe screening procedures (i.e. those procedures done to determine eligibility), including examinations and laboratory testing*
- *Specify time frame for completion of screening studies relative to time of enrollment*

If applicable, identify screening protocol to be used for this study and briefly describe what evaluations will be done under the screening protocol

C. Study Visits and Procedures

1. Participant visits and procedures

- *Describe all evaluations and timeframe for completion; include blood draw amounts*
- *Describe, in chronological order, when possible. May name visits (e.g. enrollment/baseline, study phase, follow-up)*
- *Clearly identify which procedures are solely for research purposes, which are clinical care done for evaluation or treatment of the subjects' condition, and which are both*
- *Clearly identify if radiation is used and if it is medically-indicated, for research only or both*

- *Include visits (“follow-up visits”) done after completion of study interventions (if applicable)*
- *Identify relationship to other protocols*
- *Include questionnaires or other psychological instruments and estimate how long they will take to complete, and whether they address sensitive topics (Attach as appendix)*
- *Genetic counseling (If applicable, specify by whom; would counseling happen in person; will understanding be assessed?)*

2. Laboratory evaluations, if not standard diagnostic tests

3. Explain how the return of lab results will comply with CLIA (for example, and if applicable, laboratory tests will be performed at a CLIA-certified lab, if required by applicable law.)

D. End of Participation. You should address issues such as:

1. Planned procedure for ending protocol

- Transfer of care to assure continuity of care, if applicable*
- Medical care offered at completion of study procedures, if applicable*
- State what information will be shared with subjects or their health care providers*

2. Premature withdrawal

- Provide criteria for removal of participants from study*

VI. CONSIDERATIONS FOR STUDIES INVOLVING DRUGS, DEVICES OR BIOLOGICS

A. Description of drug or device used to investigate the study

hypothesis. *If a commercially available drug is used, justify whether (or not) an IND is required. If an IND is required for commercially available or investigational agents, provide the number and identify the Sponsor. If a device is used, identify the device, justify whether an IDE is required or not, and identify the Sponsor if applicable. Provide the investigators’ brochure and address Sponsor reporting in the appropriate sections. (For more information about INDs, see NIH HRPP SOP 15 “Research Regulated by the Food and Drug Administration (FDA): General Procedures for Both IND and IDE Applications”, SOP 15A “Research Regulated by the Food and Drug Administration (FDA): Information and*

Policies Specific to Research Involving Investigational New Drugs (Including Biological Products)”or *NIH HRPP SOP 15B “Research Regulated by the Food and Drug Administration (FDA): Information and Policies for Investigational Device Exemption (IDE) Applications”*.

- B. Describe the biologic/gene to be used.**
- C. Describe the drug/other agent. Provide information on toxicity, formulation, administration, dosages and their adjustment, incompatibilities, the investigator’s brochure (for IND agents.)**
- D. Describe the device. Provide a summary of known effects, toxicities, method of administration.**

VII. STATISTICAL CONSIDERATIONS

- A. Description of the statistical analyses** *(Describe analysis to be used for primary and secondary study endpoints and any exploratory analyses, including level of significance and handling of missing or spurious data, and any planned interim analysis)*
- B. Method and timing for analyzing outcome measures**
- C. Sample size justification** *(Include accrual number request, taking into account screening failures and withdrawals)*
- D. Final analysis plan**

VIII. MONITORING OF PROBLEMS AND QUALITY ASSURANCE AND REPORTING

- A. Collection, monitoring, and analysis of changes from the protocol plan, adverse events and problems.** *(NIH HRPP SOP 16 provides detail about NIH requirements for monitoring and reporting of adverse events (AEs) and unanticipated problems (UPs.)*

Anticipated AEs and problems

- *This section should describe all potential AEs that can be anticipated and monitored for this protocol*
- *If this is either a natural history or limited encounter protocol, specify the occurrences that you wish to exclude from AE reporting. (E.g., for natural history protocols, describe range of*

medical events independent of any protocol encounter that are known to occur in subjects who qualify for study enrollment. Natural history protocols may monitor, but may not consider as reportable, occurrences that are purely a consequence of an underlying genetic or medical condition under study in a protocol.

- *Furthermore, AEs may not be ascertained in limited encounter protocols such as linkage studies or tissue array studies, in which investigators are not providers of medical services*

B. Plan to monitor and analyze events

Describe plan to monitor and report AEs for this protocol (anticipated and unanticipated, serious and non-serious) and UPs.

C. Type and duration of follow-up of subjects after UPs and/or serious adverse events (SAEs)

D. Reporting procedures

- *In this section, describe the reporting of UPs, protocol deviations and (for FDA-regulated research) SAEs. The PI can request and the IRB can approve a written plan in the protocol for not immediately reporting specified expected SAEs (for example, expected death from the underlying illness.) In addition, UPs that are not AEs should be reported to the IRB. An unanticipated problem is an event that is:*
 - *unexpected in nature, frequency or severity, and*
 - *related or possibly related to the research and*
 - *suggests that the risk of harm to subjects or others is increased*
- *Some examples of possible UPs include: theft or loss of identifiable data, product instability, freezer thaws, etc.*

E. Criteria for stopping the study or suspending enrollment or procedures

- *State what review will be done to determine if research can resume*

F. Data and Safety monitoring plan (For more information about data and safety monitoring see NIH HRPP SOP 17 “Data and Safety Monitoring.”)

- *State what parameters will be monitored for the study as a whole*
- *Frequency of monitoring (by time, cohort or study milestone)*
- *Identify who monitors the study*
- *Monitoring process should reflect study risk (e.g. monitoring can be conducted by multiple entities, including the PI, investigator, independent study monitor, independent monitoring committee, DSMB.)*

- *If a DSMB is used, describe the:*
 - *Proposed membership (or state name of existing DSMB)*
 - *Proposed charge to the DSMB*
 - *Proposed meeting frequency/schedule*

G. Quality assurance/site monitoring *(For more information about quality assurance see NIH HRPP SOP 23 “Quality Management System for the NIH HRPP”) Identify who performs or is responsible for the monitoring e.g. external auditor*

IX. HUMAN SUBJECTS PROTECTION ISSUES

A. Study Population

- 1. Justification for inclusion or exclusion of women, men, minorities, and children or other vulnerable subjects** *(Vulnerable subjects include those who lack consent capacity, the mentally ill, prisoners, cognitively impaired subjects, pregnant women, children, and employee volunteers. For more information about vulnerable subjects in research see “SOP 14A - Research Involving Vulnerable Subjects (General Considerations)”, SOP 14B “Research Involving Pregnant Women, Human Fetuses and Neonates”, SOP 14C “Research Involving Prisoners”, SOP 14D “Research Involving Children”, SOP 14E “Research Involving Adults Who Are or May Be Unable to Consent”, or SOP 14F “Research Involving NIH Staff as Subjects”)*
- 2. Justification for sensitive procedures** *(Such procedures can include: use of placebo, medication withdrawal, provocative testing, deception)*
- 3. Safeguards for protecting vulnerable populations**
- 4. Recruitment plans**
 - *Description of recruitment strategy*
 - *Source of subjects*
 - *Recruitment venues*
 - *How potential subjects will be identified and approached*
 - *Anticipated accrual rate*
 - *Types of advertisements planned (e.g. national newspaper, local flyers; specific names are not needed) Provide recruiting materials, including advertisements, list-serve notices, letters to participants or physicians, and recruitment website content, as attachments to protocol*

- *Provide pre-screening questions as attachment*

B. Reimbursement, incentives, travel reimbursement and in kind benefits

- *Describe whether participants will receive reimbursement/incentives and describe amount, form and timing of any such compensation in relation to study activities (include financial and non-financial incentives)*
- *Describe who will receive incentives (if not the subject). For example, if minors, state whether the minor or the parent/guardian will receive the incentive. If incapacitated adult, state if payment will be provided to the subject or to a guardian*
- *State if any items are provided in kind (e.g. vouchers, iPads)*

C. Risks and discomforts *(Summarize risks of the study. Describe steps taken to minimize risk).*

Risks can include:

- *Physical harms from therapeutic interventions (such as drugs/devices/gene transfer/radiation) or Diagnostic interventions (blood draws/imaging/biopsies)*
- *Psychological harms (misunderstanding, anxiety, self-esteem, depression)*
- *Risks to family relationships (related to determination of genetic/disease status, parentage, adoption)*
- *Discrimination (insurance, employment)*

D. Potential benefits

- *Describe whether the study has the potential for direct benefits to participants (include only those physical or psychosocial benefits that derive directly from an intervention being studied)*
- *Describe any collateral benefit to participants (for example, medical or genetic counseling care and other benefits associated with being a research subject that are not directly related to the specific study intervention. Do not include financial compensation as a direct or collateral benefit)*
- *Benefits to society (describe whether the study is likely to yield generalizable knowledge)*

E. Classification of risk for the study as a whole

- *For example, for research with Adults, classify as minimal risk OR more than minimal risk*

- *For Adults without consent capacity (if applicable)NIH HRPP SOP 14E “Research Involving Adults Who Are or May Be Unable to Consent,” provides some suggestions for classifying risk.*
- *For Children, classify as one of the following:*
 - *45 CFR 46.404 Research that does not involve greater than minimal risk*
 - *45 CFR 46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child*
 - *45 CFR 46.406 Research involving no greater than a minor increment over minimal risk and no prospect of direct benefit but likely to yield generalizable knowledge*
 - *45 CFR 46.407 Research not approvable under classifications above, but presenting a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem affecting the health or welfare of children*
(NOTE: An IRB cannot approve research under 45 CFR 46.407, unless the Secretary of DHHS also provides approval. For more information see NIH HRPP SOP 14D “Research Involving Children”)

- F. Assessment of Risk/ Benefit ratio** (for more information about risk and benefit, see SOP 4 “Human Research Protection Program (HRPP) Documentation and Records”, Appendix B “NIH Protocol Review Standards”.)
- *Describe overall balance of risk and benefit considerations, state whether the risks are reasonable in relation to anticipated benefit*

G. Alternatives to participation or alternative therapies

- *Treatment/ therapeutic alternatives should be discussed. State if none..*

H. Subject Confidentiality (“For more information about confidentiality and privacy, see NIH HRPP SOP 18 “Privacy and Confidentiality.”)

- *Describe protections for maintaining confidentiality of subject data, forms, records and samples, etc.*

1. For research data and medical records

- *Describe whether identifiers will be attached to data, or whether data will be coded or unlinked*
- *If unlinked or coded, and additional information (age, ethnicity, sex, diagnosis) is available, discuss whether this might make specific individuals or families identifiable*

- *If research data will be coded, how will access to the “key” for the code be limited? Include description of security measures (password-protected database, locked drawer, other). List names or positions of persons with access to the key*
 - *Under what circumstances will data/samples be shared with other researchers?*
 - *Will pedigrees be published? Include description of measures to minimize the chance of identifying specific families*
 - *Will personally identifiable information be released to third parties?*
 - *State who has access to records, data, and samples. Consider if monitors or auditors outside of study investigators will need access*
 - *Discuss any additional features to protect confidentiality (such as use of a certificate of confidentiality, etc.)*
- 2. For stored samples - including sharing samples and PII.** *(For more information about working with human specimens or data see SOP 5 “NIH Research Activities with Human Data/Specimens”.)*
- *Will participant identifiers be attached to samples, or will samples/data be coded or unlinked from identifiers?*
 - *Description of any clinical/demographic information that will be included (age, ethnicity, sex, diagnosis, stage, treatment)*
 - *How might this information make specific individuals or families identifiable?*
 - *Under what circumstances will data/samples be shared with other researchers?*
- 3. Research use of stored human samples, specimens or data.** *Address each of the items listed below. (For more information about working with human specimens or data see SOP 5 “NIH Research Activities with Human Data/Specimens”.)*
- *Intended Use: Example language (may not be applicable to a particular study): Samples and data collected under this protocol may be used to study [XX]. [No] genetic testing will be performed.*
 - *Storage: State whether samples or data will be retained, list type of samples and location of storage. There are many acceptable approaches to data storage. An example of language for describing data storage is as follows: “ Access to stored samples will be limited using [either a locked room or a locked freezer]. Samples and data will be stored using codes assigned by the investigators. Data will be kept in password-*

protected computers. Only investigators will have access to the samples and data.”

- *Tracking: Describe method of tracking, such as the name of the software tracking program or other logging/tracking method*
 - *Disposition at the Completion of the Protocol: (Describe the disposition of the specimens, the protocol will remain open, they will be sent to a repository, etc... as applicable) There are multiple approaches for disposition of samples after research is conducted.*
 - *Approach for responding to requests from subjects for destruction of samples (if applicable)*

I. Informed Consent Process *(Consult with the IRB regarding enrollment of non-English speakers, and, if appropriate, use of long-form translated consent documents or a short-form consent document.)*

1. Consent/assent documents and other informational items provided to subjects

- *Confirm whether the consent form contains all required regulatory elements*
- *List all consent documents and materials submitted with this protocol*
 - *(Include consent and/or assent forms, printed or web-based materials, phone scripts and any other related material.)*
- *If needed, describe special documents or materials (Braille, another language, audiotape, etc.)*

2. Designation of those obtaining consent/assent

3. Assent and/or consent procedures and documentation

- *Describe how informed consent will be administered. Describe any proposed waivers or alterations to informed consent. Describe any special circumstances regarding obtaining consent. Describe plans for obtaining consent from speakers of languages other than English.*
- *One example of possible language in this section is as follows: “All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions regarding this study prior to signing.”*

X. ADDITIONAL NIH REQUIREMENTS

A. Study Staff Roles and Qualifications

For individuals at non-NIH sites, include the name of the site, FWA# and contact information. For more information about collaborations see NIH HRPP SOP 20 "NIH HRPP Requirements for Collaborative Research".

- *Identify each investigator by name and include credentials*
- *Identify role in study*
- *State qualifications to perform the study role*
- *Investigators with similar roles and qualifications can be described as a group*

B. Conflict of Interest (*For more information about conflict of interest requirements see NIH HRPP SOP 21 "Conflict of Interest Requirements for Researchers and Research Staff".*)

- *Confirm whether investigators will abide by their own institutional conflict-of-interest policies*
- *If applicable, describe the role of a commercial company or sponsor. If there is a commercial company or sponsor for the study, state what the company/ sponsor will provide to the institution and what the institution will provide to them. State if personal identifiers of participants will be shared with the sponsor*

C. Technology transfer

- *List any tech transfer, material transfer, or any confidential disclosure agreement/s and the parties involved*

XI. REFERENCES

XII. APPENDICES/ATTACHMENTS (as applicable)

- A.** Flow sheets
- B.** Eligibility checklist
- C.** Case report forms (CRFs)
- D.** Rating scales and questionnaires
- E.** Recruiting materials
- F.** Screening questionnaires for Patient Recruitment Office
- G.** Other

ATTACHMENT 3: INITIAL REVIEW LOCAL CONTEXT WORKSHEET

Initial Review Local Context Worksheet

Please complete a copy of this worksheet for each relying institution. This form should be completed by the Site PI and, if the PI and institution choose to delegate one, the local context representative. The local context representative is typically an individual with knowledge of the institutional human research protection program and its policies as well as state law. Answers pertain to the implementation of the protocol named below at your institution.

Date of Submission: _____(DD/MM/YY)

Principal Investigator	
Protocol Title	
Protocol #	
Institution Relying on NIH for IRB Review (signatory institution):	
Local Context Representative (optional)	
Title of Local Context Representative (optional)	

SUBJECT SELECTION

1. Does the selection and recruitment process for this protocol comply with local laws and your institutional policies?

Yes

No *(If no, please attach an explanation to this form.)*

2. Do you find the selection and recruitment methods in this protocol acceptable in the context of your local area?

- Yes
- No *(If no, please attach an explanation to this form.)*

3. Is there anything else the PHERRB should know about the anticipated study population at your institution?

- Yes *(If yes, please attach an explanation to this form.)*
- No

VULNERABLE POPULATIONS

Note about prisoners: THE PHERRB is not constituted to review research about prisoners. If an investigator wishes to enroll prisoners in a study, IRB review must be conducted by the local IRB.

4. Check all vulnerable populations from which you intend to enroll in this protocol. Will there be vulnerable groups among the study population?

- Children
- Pregnant women
- Adults with impaired decision making capacity
- Emancipated minors, mature minors
- Wards of the state
- Other special populations. Please describe: _____

5. Will non-English speakers be enrolled?

- Yes
- No *(If no, please attach an explanation to this form.)*

INFORMED CONSENT PROCESS

6. Does the consent/assent process for this protocol comply with local laws and your institution's consent policies?

- Yes

No *(If no, please attach an explanation to this form.)*

7. Do the consent/assent documents (and/or waiver of consent of documented consent) for this protocol comply with local laws and your institution's policies regarding informed consent?

Yes

No *(If no, please attach an explanation to this form.)*

8. According to the protocol, who will provide consent or parental permission? *(check all that potentially apply)*

Potential study participant

Parent of potential pediatric study participant

Legally Authorized Representative (LARs)

Other: Please describe: _____

9. If non-English speakers will be enrolled, describe how the recruitment and informed consent process will be conducted? *(If applicable, an attachment may be added.)*

COMPENSATION

10. Will you provide compensation to participants enrolled in this protocol?

Yes

No *(If no, please attach an explanation to this form.)*

11. Is the participant compensation described in the protocol consistent with local laws and your institution's policies?

Yes

No *(If no, please attach an explanation to this form.)*

PRIVACY AND CONFIDENTIALITY

12. Are the privacy and confidentiality provisions of the protocol consistent with the resources and practices available at your institution?

- Yes
- No *(If no, please attach an explanation to this form.)*

13. Are the privacy and confidentiality provisions of the protocol consistent with local laws, institutional policies, and HIPAA (if applicable)?

- Yes
- No *(If no, please attach an explanation to this form.)*

14. Are there any other sections of the protocol which are inconsistent with local laws or your institution's policies?

- Yes *(If so, please attach an explanation to this form.)*
- No

COMMUNITY DESCRIPTORS

15. Given the nature of this particular research study, are there any additional factors particular to this study site or the community (community attitudes, ethnic diversity, language, etc.) that may contribute to the acceptability of this research in your area?

- Yes *(If so, please attach an explanation to this form.)*
- No

16. Does the community have a positive attitude toward the conduct of research?

- Yes
- No *(If no, please attach an explanation to this form.)*

STATE AND LOCAL LAW

17. List the states from which you will be recruiting and provide the age of majority for each state. *(If applicable, an attachment may be added.)*

18. If consent will be provided by LARs, describe your state and local law, and corresponding institutional policy regarding LARs. Describe who may serve as an LAR according to state laws and institutional policies. *(If applicable, an attachment can be added.)*

19. If children or adults who are decisionally impaired will be enrolled, describe your state, local, and corresponding institutional policies regarding assent by children or adults who are unable to provide consent. *(If applicable, an attachment can be added.)*
20. If mature or emancipated minors will be enrolled, please describe the circumstances under which they will be able to provide consent to their own participation and describe any applicable state, local, and institutional policies.
21. If wards of the state or other special populations (child or adult) will be enrolled, describe any applicable state, local, or institutional policies if they have requirements that go beyond what is required in the corresponding subparts of 45 CFR 46. *(If applicable, an attachment can be added.)*
22. What are the other state and local laws that govern the conduct of research at your institution? *(If applicable, an attachment can be added.)*

ADDITIONAL INFORMATION

23. Describe your institution's process to receive and address concerns from study participants and others about the conduct of the research. *If applicable, an attachment may be added.*
24. Add any additional comments that will help the PHERRB in its review process: *(If applicable, an attachment may be added.)*
25. Describe how the relying institution gathers and evaluates the PI and research staff for financial conflicts of interest. *(If applicable, an attachment may be added.)*
26. Please describe your institution's requirements for human subject protections training for PIs and other staff engaged in research.
27. Provide the boilerplate language that is specific to your institution. This is standard language required by the institution that is inserted into the existing CIRB-approved informed consent document, such as: birth control language, coverage of research injury, required phone numbers for the PI or Study representative, and a person unaffiliated with the study who can answer general study questions, etc. *(If applicable, an attachment may be added.)*

28. Provide the institutional letterhead used for the informed consent document. *(If applicable, an attachment may be added.)*

29. Provide any other institutional requirements for informed consent documents. *(If applicable, an attachment may be added.)*

30. Is there anything else the PHERRB should know about the institution's local context or institutional policies?

Yes

No

ATTACHMENT 4: CONTINUING REVIEW LOCAL CONTEXT WORKSHEET

This form should be completed by the Site PI. The topics listed below reflect those asked on the Initial Review Local Context Worksheet that was previously submitted for the protocol named below. Indicate for each topic whether or not there are changes from the information previously provided. If there are changes, please describe. Attachments in support of changes may be added.

Date of Submission: _____(DD/MM/YY)

Principal Investigator	
Protocol Title	
Protocol #	
Institution Relying on NIH for IRB Review (signatory institution)	
Local Context Representative:	

SUBJECT SELECTION (Questions 1-3 on the Initial Review Local Context Worksheet)

- No change
- Changed (If changed, please attach an explanation to this form.)

VULNERABLE POPULATIONS (Questions 4-5 on the Initial Review Local Context Worksheet)

- No change
- Changed (If changed, please attach an explanation to this form.)

INFORMED CONSENT PROCESS (Questions 6-9 on the Initial Review Local Context Worksheet)

- No change
- Changed (If changed, please attach an explanation to this form.)

COMPENSATION (Questions 10-11 on the Initial Review Local Context Worksheet)

- No change
- Changed (If changed, please attach an explanation to this form.)

PRIVACY AND CONFIDENTIALITY (Questions 12-14 on the Initial Review Local Context Worksheet)

- No change
- Changed (If changed, please attach an explanation to this form.)

COMMUNITY DESCRIPTORS (Questions 15-16 on the Initial Review Local Context Worksheet)

- No change
- Changed (If changed, please attach an explanation to this form.)

STATE AND LOCAL LAW (Questions 17-22 on the Initial Review Local Context Worksheet)

- No change
- Changed (If changed, please attach an explanation to this form.)

ADDITIONAL INFORMATION (Questions 23-30 on the Initial Review Local Context Worksheet)

- No change
- Changed (If changed, please attach an explanation to this form.)