P&P: RR 410 Version No: 1.3 Effective Date: 12/06/2024	PROTOCOL DEVIATIONS AND NONCOMPLIANCES	Supercedes: CPHS Policies and Procedures 06/30/2023

1. POLICY

Deviation from an IRB-approved protocol, as well as noncompliance with applicable University policies, regulatory requirements, and/or IRB determinations, must be reported to the IRB. Such occurrences can have a negative impact on research participants. Protocol deviation and noncompliance can alter the risk-benefit ratio for participants or otherwise jeopardize the safety, rights, and welfare of subjects. Nevertheless, there are also times when it is necessary to deviate from the approved research plan or continue aspects of the research during a lapse in approval in order to protect research subjects.

Reported incidents will be considered *possible* noncompliance until a final determination is made by the IRB. The IRB will assess the severity of the event and, if necessary, require corrective action. Serious and continuing noncompliance will be reported to the appropriate institutional officials and regulatory agencies as applicable.

Specific Policies

1.1 Definitions

1.1.1 *Noncompliance*. Failure to comply with the requirements of an applicable law, regulation, or institutional policy pertaining to the protection of human subjects, and/or with the requirements or determinations of an IRB. In addition, failing to submit a continuing review application in a timely manner, which results in the IRB approval expiring, is considered noncompliance for the PI. However, it is not noncompliance when there is a need to deviate from the approved protocol or continue aspects of the research after expiration of approval in order to protect the welfare of research participants, as described below in 1.3 Special Considerations. Also, departure from the protocol that is due to a study participant's non-adherence is not considered to be a protocol deviation but may need to be reported to the IRB per RR 408 – Unanticipated Problems and Adverse Events.

1.1.2 *Simple (Minor) Noncompliance*. These are incidents which are the result of an unintentional deviation or omission from the protocol that the IRB has approved or determined to be exempt. A minor noncompliance shall not have negatively affected the rights, safety, or welfare of the subjects. The conduct of unsubmitted or unreviewed human subjects research that would have qualified for an exempt determination had it been reviewed and determined exempt by the IRB staff in advance of initiating the research will also be considered a simple noncompliance.

1.1.3 *Serious Noncompliance.* Noncompliance that adversely affects the rights or welfare of participants. These are incidents of noncompliance involving non-exempt protocols where: the noncompliance increases the risk and/or decreases the benefit to individual subjects; the research takes place without appropriate IRB review and approval; egregious or intentional noncompliance occurs; and/or another situation exists which the convened CPHS Executive Committee

or IRB determines to be a serious noncompliance.

1.1.4 *Continuing Noncompliance.* A pattern of noncompliance that indicates an inability or unwillingness to comply with the requirements of an applicable law, regulation, or institutional policy pertaining to the protection of human subjects and/or with the requirements or determinations of an IRB.

1.1.5 *Protocol Deviation.* Any change, divergence, or departure from the study design or procedures defined in the approved protocol (FDA CP Clinical Investigators and Sponsor-Investigators, p. 22, 2008). Protocol deviations may or may not be considered noncompliance, per 1.1.1 above.

1.2 Reporting Requirements and Procedures

1.2.1 Reports by the investigator:

(1) In general, protocol deviations and noncompliance should be reported to the IRB as soon as possible. An initial report should be made to the OPHS Director within *1 week* (7 calendar days) of when the investigator became aware of the event. When the deviation is subject to FDA's device regulations, the investigator must notify the sponsor and the IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred (21 CFR 812.150(4)).

(2) The initial report must be followed by a formal eProtocol Deviation Report within no more than *2 weeks* (14 calendar days) of when the investigator became aware of the event.

(3) In some cases, reporting requirements may be met by submitting a preliminary report to the OPHS Director, IRB, and other officials/agencies involved, with a follow-up report submitted at a later date when more information is available. These determinations will be made on a case-by-case basis, with the IRB Chair, OPHS Director, investigator, institutional official(s) and/or others involved as appropriate. The primary consideration in making these judgments will be the need to take timely action to prevent avoidable harms to subjects and others.

1.2.2 Reports of potential deviations and/or noncompliance by other parties (e.g., research staff, general public, research subjects, etc.):

(1) Whenever possible, reports should be submitted via the investigator. However, if the reporting party deems it necessary and/or wishes to remain anonymous to the investigator, they may contact OPHS directly.

(2) Protocol deviations and noncompliance may also be reported using the University-wide whistleblower hotline.

(3) Protocol deviations and/or noncompliance incidents may be discovered by CPHS members or OPHS staff as part of continuing review of nonexempt protocols, as part of a Quality Assurance or audit activity, or an incidental awareness (e.g., due to a news article, errant email, or incidental finding

of recruitment material). Such discoveries must be promptly reported to the OPHS Director.

(4) Individuals may also directly report suspected deviations and/or noncompliance to the Office for Human Research Protection (OHRP), the human subjects research oversight agency.

1.2.3 The reporting party should use their judgment when determining if an event is reportable. If an individual is unsure of whether there are grounds to report an event, they may call upon the OPHS Director or Assistant Director to discuss the situation informally.

1.2.4 Alternatively, individuals always have the option of making reports through the Whistleblower process. A protected disclosure is a good faith communication about an incident that might constitute improper governmental activity or may significantly threaten the health or safety of employees or the public, if the disclosure or intention to disclose was made for the purpose of remedying that condition. Reports of possible noncompliance should include a complete description of the event and include sufficient detail to allow the IRB to make an assessment.

1.3 Special Considerations

1.3.1 Deviations from the IRB approved protocol that cannot wait for IRB review because of the immediate need to eliminate apparent hazards to the subject are not considered noncompliance per RR 404 – Amendment (Revision) Review.

1.3.2 The continued participation of enrolled subjects in research for which approval has expired is also not considered noncompliance per RR 403 – Continuing Review if it is necessary to protect the best interests of enrolled subjects.

1.3.3 The determination of whether it is necessary to deviate from the approved protocol or to continue aspects of the research to protect subjects may initially be made by the investigator. This determination may be made for enrolled subjects as a group or for individual subjects. However, the investigator must submit a report to request IRB confirmation of agreement as soon as possible (see 1.2.1 above).

1.4 IRB Review and Actions

The IRB will fully investigate and review reports of possible noncompliance to determine if the event was (1) not noncompliance, (2) simple noncompliance, (3) serious noncompliance, or (4) continuing noncompliance. See Section 4 for process details. If necessary, the IRB will require corrective action. The IRB will attempt to resolve alleged instances of noncompliance without interrupting the conduct of the study, especially if the rights, safety, and welfare of subjects may be jeopardized by the interruption. All reports of potential noncompliance as well as the outcome of investigations that are substantiated will be noted in the protocol record.

1.4.1 If the IRB finds that no noncompliance occurred because: (1) the reported noncompliance was unsubstantiated, (2) the investigator deviated from the protocol in order to eliminate immediate and apparent hazards to subjects, or (3) continued participation of enrolled subjects in research for which approval has expired was necessary to protect the best interests of enrolled subjects, actions by the IRB may include but are not limited to:

- Requiring no further action.
- Requiring submission of an amendment to the protocol or consent form.
- Requiring submission of a continuing review application.
- Permitting or disallowing use of data collected during (2) and (3) above.

1.4.2 If simple noncompliance is found to have occurred, actions by the IRB Chair/Vice Chair or OPHS Director may include but are not limited to:

- Requiring no further action.
- Requiring remedial training (e.g., online educational program, attendance at workshop, one-on-one training).
- Requiring re-consent of subjects.
- Requiring the submission of an amendment to the protocol or consent form.

Whenever appropriate, investigators will be assisted so that they can achieve compliance without the need for sanctions. However, if the investigator fails to cooperate with IRB requests to correct minor noncompliance, this inaction will be treated as continuing noncompliance.

1.4.3 If serious and/or continuing noncompliance is found to have occurred, actions by the IRB may include but are not limited to:

- Establishing a corrective action plan.
- Asking the investigator to voluntarily halt the research until they are in compliance.
- Requiring the investigator to participate in and complete further training.
- Requiring more frequent review of the project.
- Permitting or disallowing use of the data collected during noncompliance.
- Not permitting publication or dissemination of the results of the research.
- Limiting the investigator's human subject research privileges.
- Writing letters of censure.
- Making recommendations to the Institutional Official (IO) for further sanctions, stipulations, or restrictions to investigator's privilege to conduct human subjects research.
- Sharing information of noncompliance with other institutional units (e.g., Conflict of Interest Committee, Research Integrity Officer) as deemed necessary.

1.4.4 The IRB and, when appropriate, the institution will act promptly to ensure remedial action regarding any breach of regulatory or institutional human subject protection requirements. The IRB also has the authority to suspend or

terminate approval of research that is not being conducted in accordance with the IRB policies, is not in compliance with federal regulations, or deviates from the approved protocol (see RR 409 – Suspension or Termination of Human Research).

1.4.5 All serious and/or continuing noncompliance must be reported promptly to the Assistant Vice Chancellor for Research Administration and Compliance (AVC-RAC), the Institutional Official (IO) and, for federally funded research, the appropriate department, agency head or sponsor. Reports will only be made to OHRP and/or FDA for research that is regulated by these oversight agencies per UC Berkeley's Federalwide Assurance (FWA). Copies of reports or correspondence sent to outside agencies will be maintained by the OPHS Director.

2. SCOPE

These policies and procedures apply to all human subjects research conducted by UC Berkeley.

3. RESPONSIBILITY

The investigator, or other reporting party, is responsible for reporting observed or apparent protocol deviation or noncompliance in good faith, maintaining confidentiality, and cooperating with any internal inquiries.

OPHS staff, the IRB Chair, the AVC-RAC, and/or the UCB Whistleblower hotline are the persons or unit who may receive allegations of noncompliance, reports, or concerns about the conduct of human subjects research, and forward the information on to the OPHS Director for review.

The OPHS Director reviews the potential noncompliance and determines whether it requires IRB Chair review. If IRB Chair review is required based on this policy, the OPHS Director (or designee) is responsible for assisting the IRB Chair with fact gathering and review of the possible noncompliance. OPHS staff facilitate review of the possible noncompliance and maintain records related to the incident. The OPHS Director or IRB Chair (if appropriate) reviews the potential noncompliance and may take one or more actions such as, but not limited to, convening an ad hoc subcommittee to conduct a more extensive investigation and/or asking the convened IRB to make a decision. Incidences of potential serious or continuing noncompliance will generally be referred to the convened IRB for deliberation and a final decision on the process and/or the outcome. Alternatively, based on a deviation or noncompliance report, the OPHS Director may decide that the potential noncompliance should be discussed by the convened CPHS Executive Committee.

The convened CPHS Executive Committee and/or IRB reviews information gathered about the possible noncompliance, reviews pertinent data or findings of the investigation, deliberates, and makes a decision about the nature of the incident and course of action. The CPHS Executive Committee may also decide that an additional ad hoc IRB subcommittee is needed to review the incident.

The ad hoc IRB subcommittee (if appointed by the Chair or Executive Committee) reviews

the possible noncompliance, conducts interviews and hearings as needed, reviews pertinent data or findings of the investigation, deliberates, and makes recommendations to the Executive Committee and/or convened IRB as to a course of action.

The OPHS Director (or OPHS designee on their behalf) will inform the PI of the IRB decision and will confirm that corrective action has been taken (if applicable. The OPHS Director is also responsible for notifying the AVCR-RAC and IO about any serious or continuing noncompliance and will cooperate in notifying a federal funding agency and/or other regulatory bodies about the noncompliance, as appropriate.

4. PROCESS OVERVIEW

Reports of noncompliance may be received through any number of means, including but not limited to, by an OPHS staff member, IRB Chair, or AVC-RAC, via mail/delivery, phone, email, eProtocol, or during an office or site visit.

The OPHS Director, in consultation with the IRB Chair, if appropriate, determines if the potential noncompliance was (a) not noncompliance, (b) simple noncompliance; or, (c) serious noncompliance and/or continuing noncompliance. If deemed potentially serious or continuing, the IRB Chair may convene an ad hoc subcommittee to conduct an investigation. Otherwise, the IRB Chair and the OPHS Director (or designee) will proceed to investigate the incident.

Based on the findings of an investigation, the IRB Chair will make a decision on the action to be taken or ask the convened CPHS Executive Committee and/or IRB to make a decision. Incidences of serious or continuing noncompliance will generally be referred to the convened IRB for a decision.

The OPHS Staff will notify the investigator of the review outcome in writing promptly.

If the IRB determines that the noncompliance is serious and/or continuing, the IRB Director reports this in writing to the IO and the Assistant Vice Chancellor for Research Administration and Compliance along with any further recommendations from the IRB for potential institutional action. Regulatory authorities or Sponsors may also be notified by the IO (or his or her designee) as applicable and required.

5. APPLICABLE REGULATIONS AND GUIDELINES

21 CFR 56.109, 21 CFR 56.113, 21 CFR 56.120, 21 CFR 812.150, 21 CFR 312.66

45 CFR 46.109, 45 CFR 46.113

Compliance Program Guidance Manual, Program 7348.811, Chapter 48 – Bioresearch Monitoring, Clinical Investigators and Sponsor-Investigators, December 8, 2008.

SACHRP Recommendations on Protocol Deviations

UCB Policy on Research Misconduct