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| California Pacific Medical Center (CPMC) | Standard Operating Procedure | |
| Institutional Review Board (IRB) | Investigator Reporting and IRB Review of Protocol Violations and Deviations | July 22, 2010 |

Purpose

This Standard Operating Procedure (SOP) is to document the policies and procedures for the Principal Investigator's (PI) reporting of protocol violations, protocol deviations and protocol exemptions for research operating under the approval of the California Pacific Medical Center Institutional Review Board (IRB). It also provides guidance for the CPMC IRB in the review of reports of protocol deviations and violations.

This SOP complies with U.S. Department of Health and Human Services (DHHS) regulations 45 CFR 46 (Common Rule), Food and Drug Administration (FDA) 21 CFR 56, and DHHS 45 CFR 160 and 164 Subpart E, Standards for Privacy of Individually Identifiable Health Information as well as CPMC's Federalwide Assurance (FWA).

Definitions

The following definitions are critical to understanding this SOP:

- **Protocol Deviation:** A departure from the IRB-approved research plan that does not involve an actual threat to the health, safety and welfare of a research participant, and has no substantive effect on the value of the data collected. Examples of protocol deviations include, but are not limited to: missed lab draws, missed study assessments (e.g., vital signs), or a scheduling error made by a member of the research team. A series of protocol deviations could be classified as a protocol violation.
- **Protocol Exemption:** A prospectively approved protocol departure granted by a study sponsor that does not increase the risk to participants (e.g., minor exceptions to the inclusion/exclusion criteria or an exception to the treatment schedule), also referred to as a protocol exception.
- **Protocol Violation:** A departure from the IRB-approved research plan that may, or does, put at risk the health, safety, welfare, and privacy of a research participant or the integrity of the study. Examples of protocol violations

include, but are not limited to: consent form errors, breaches of confidentiality, investigational drug or other medication errors, inclusion/exclusion errors, and randomization errors.

Definitions of other pertinent terms are in the IRB Mater Glossary found on the CPMC IRB Web site at: <http://www.cpmc.org/research/irb/>

Policies

1. CPMC investigators will conduct studies involving research subjects in full compliance with the research protocol approved by the CPMC IRB.
2. If a protocol deviation or violation results in an adverse event (AE) or serious adverse event (SAE), the event will be reported to the IRB according to CPMC IRB SOP Adverse Events, Serious Adverse Events, and IND Safety Reports: Principal Investigator Reporting Requirements.
3. For the purpose of this SOP, the failure of a research subject to adhere to the protocol is **not** considered a protocol violation or deviation.
4. The PI will report a **protocol violation**, as defined in the CPMC IRB Glossary, to the IRB as soon as possible, but no later than 10 business days following discovery of the event.
5. All **protocol violations** will be reviewed by the convened IRB at the earliest opportunity.
6. All **protocol deviations**, as defined in the CPMC IRB Glossary, will be reviewed by the IRB at the time of continuing review (on Violation/Deviation/Exemption Summary Grid).
 - 6.1. If the study otherwise qualifies for expedited review at continuing review, an expedited review procedure can be conducted.
 - 6.2. If a departure from the protocol is made to eliminate an immediate hazard or risk to the research subject, the CPMC PI will report the change, including the reason for the departure, to the IRB within 10 business days following the discovery.
7. The classification of a protocol departure as a deviation or violation will be based on the PI's judgment (unless it is clearly defined in the protocol). The IRB will make the final determination as to whether the incident is a protocol deviation or violation.
8. CPMC investigators will not implement any change to an IRB-approved protocol without first obtaining IRB approval of a protocol amendment, except where a

protocol change is necessary to eliminate an immediate hazard or risk to the research participant.

9. The CPMC PI may proceed with a **protocol exemption** that is granted in writing by the study sponsor, and report it to the IRB at the time of continuing review.
10. The IRB will report the following actions to the appropriate federal agencies and/or institutional officials:
 - Suspension or termination of a protocol (including study enrollment)
 - Unanticipated problems involving risks to research subjects; and
 - Serious or continuing noncompliance with federal regulations or IRB requirements.
11. The CPMC IRB will make available its policies and procedures regarding protocol violations and deviations to CPMC investigators, research staff, IRB members and IRB staff.

Procedures

1. Reporting Protocol Violations

- 1.1. As soon as possible, but no more than 10 business days following discovery of the event, the CPMC PI will submit a written report of a protocol violation to the IRB (see *Principal Investigator Protocol Violation Report Form*).
 - 1.1.1 At the time of continuing review, the CPMC PI will provide a written summary (*Violation/Deviation/Exemption Summary Report form*) to the IRB of all protocol violations, including those previously reported.
- 1.2. The IRB Administrator or IRB Coordinator may decide to notify the IRB Chair or an IRB member in the Chair's absence, of the protocol violation.
- 1.3. The IRB Chair or IRB staff may contact the PI to obtain additional information and/or to ask the investigator to stop one or more research activities, if appropriate, until the full IRB meets at a convened meeting.
 - 1.3.1. The IRB Chair may convene an emergency meeting of the IRB to address concerns raised by the protocol violation.
 - 1.3.2. The IRB Chair may require the PI to attend the meeting in person or by phone.

- 1.3.3. The IRB Chair may ask the PI to take corrective action before the next scheduled convened IRB meeting.
- 1.3.4. The IRB Chair may require the PI to provide additional information in writing for submission to the IRB.
- 1.3.5. If the protocol violation caused a serious adverse event, the IRB Chair may inform the PI of the requirement to submit an Adverse Event Report for IRB review.

2. IRB Review of Protocol Violations

- 2.1. The convened IRB will review the protocol violation report and make the following determinations, which will include at least the following:
 - a. Did the violation expose any research subject to actual or potential physical, psychological, social, or economic harm?
 - b. What was the cause and severity of the violation?
 - c. Is a PI corrective action plan required?
- 2.2 The IRB will determine the actions to be taken, which may include the following:
 - a. Requesting additional information from the PI or others;
 - b. Requiring a modification to the protocol and/or consent form;
 - c. Requiring the PI to provide all research subjects with new information regarding the study;
 - d. Requiring the PI and others involved in the research to participate in additional training;
 - e. Conducting a site visit (may be delegated to an IRB member or another individual);
 - f. Conducting more frequent IRB monitoring (e.g., requiring more frequent progress reports);
 - g. Notifying CPMC officials, sponsors and/or federal agencies; and/or
 - h. Suspending or terminating the study to protect the subjects.

3. Reporting Protocol Deviations

3.1. At the time of continuing review, the CPMC PI will provide a written summary to the IRB of all protocol deviations (as well as all previously reported protocol violations) (see *Violation/Deviation/Exemption Summary Report* form).

4. IRB Review of Protocol Deviations

4.1. The IRB will review the report summary and determine any corrective actions to be taken, which may include, but are not limited to:

- a. Requesting additional information from the PI or others;
- b. Requiring a modification to the protocol;
- c. Requiring the PI to develop a corrective action plan;
- d. Requiring the PI to provide all subjects with new information regarding the study ;
- e. Requiring the PI and others involved in the research to participate in additional training; and
- f. Notifying the CPMC Institutional Official of action taken, if appropriate.