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1414 Kuhl Ave.
Orlando, Florida 32806
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Type of Policy:	***PROTECTION OF HUMAN RESEARCH PARTICIPANTS***	Category:	**Orlando Health Institutional Review Board (IRB)**
Title:	***Protocol Deviations/Violations/ Non-compliance***	Policy #:	**0330-1001**
		Replaces #:	ORMC IRB# 6000-307 MDA IRB# 1000-0001-S
Page:	1 of 4	Developed By:	Orlando Health Institutional Review Board (IRB)
Issue Date:	**1/22/08**	Approved By:	Philip Giordano, MD Institutional Official
Revision Dates:	5/10/11, 9/10/12, 8/29/16, 1/16/17, 1/19/18, 1/19/21, 1/16/24		**SIGNATURE ON FILE**

I. PURPOSE:

The purpose of this policy is to provide reporting requirements for protocol deviations and/or non-compliance and a procedure for reviewing these reports for the Orlando Health Institutional Review Boards (IRB).

II. DEFINITIONS:

When used in this policy these terms have the following meanings:

A. Protocol Deviation - A protocol deviation is any change, divergence, or departure from a research protocol that is under the investigator's control and that has not been previously approved by the IRB.

B. Major Protocol Deviation/Violation - A protocol deviation which meets **any** of the following criteria:
   1. Potentially places the subject (or others) at a greater risk of harm (rights, well-being and/or welfare),
   2. Potentially violates ethical principles,
   3. Potentially has a major impact on the integrity of study data or the scientific design of the study,
   4. Resulted from willful or knowing misconduct on the part of the Investigator(s) or their study team (See Attachment A – Major Protocol Deviations/Violations & Regulatory Non-Compliance Examples)

C. Minor Protocol Deviation - A protocol deviation that does not fit the Major Protocol Deviation definition.

D. Regulatory Non-compliance - In some cases, problems from the conduct of the study may not be considered protocol deviations/violations but are still required to be reported to the IRB. Failure to comply with any of the federal and/or state regulations or institutional policies governing human subjects research that, in the judgment of the Orlando Health IRB, may potentially compromise human subjects protection or the integrity of the Orlando Health IRB's human subjects protection program results in Regulatory Non-compliance.

E. Serious non-compliance - Non-compliance that adversely affects the rights or welfare of research participants.

F. Continuing non-compliance - A pattern of non-compliance 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.

G. Unanticipated Problem - any incident (including deviations and/or non-compliance), 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.

III. POLICY:

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It is the policy of the IRB that any serious Protocol Deviation/Violation or any serious or continuing non-compliance involved in the conduct of human subjects' research be reported promptly and accurately. The report must be detailed for it will be reviewed by the Board and/or IRB Chair/Vice Chair/IRB Designee. The IRB will issue an appropriate action relative to its level of severity. The Corporate Office of Research Operations (CORO) is responsible for handling suspicions allegations or detected non-compliance within the research community at Orlando Health. When non-compliance is alleged, further information will be obtained by the CORO to determine whether the allegation is true.

IV. PROCEDURE:

A. Minor Protocol Deviation reporting requirements

1. A Minor Protocol Deviation is a protocol deviation that meets **all** of the following criteria:
   a. Does not have the potential to place the subject's (or others) rights, safety, or well-being at a greater risk of harm,
   b. Does not violate ethical principles,
   c. Does not have a major impact on the integrity of study data or the scientific design of the study, and
   d. Does not result from willful or knowing misconduct on the part of the Investigator(s) or their study team.
2. Minor Protocol Deviations shall be reported at the time of Continuing Review (refer to the Continuing Review Application for further guidance).

B. Major Protocol Deviation/Violation reporting requirements:

1. If the protocol deviation/violation meets **any** of the following criteria, it may be considered an unanticipated problem:
   a. Potentially places the subject (or others) at a greater risk of harm (rights, well-being and/or welfare),
   b. Potentially violates ethical principles
   c. Potentially has a major impact on the integrity of study data or the scientific design of the study,
   d. Resulted from willful or knowing misconduct on the part of the Investigator(s) or their study team
2. A Major Protocol Violation/Deviation Form must be submitted to the IRB within **5 working days** from the time any study team member (including the Investigator) becomes aware of the deviation.
3. An explanation from the Principal Investigator describing corrective actions to prevent future occurrences is also required.

C. Regulatory Non-compliance reporting requirements:

1. Once an activity has been determined to be Regulatory Non-compliance that could most likely be serious or continuing non-compliance, the Major Protocol Violation/Deviation form should be used and submitted to the IRB via IRBNet within **5 working days**. At the IRB's discretion, an explanation from the Principal Investigator describing corrective actions may also be required.

2. For instances involving expired studies (i.e., studies that have lapsed in IRB approval), the procedures outlined in the *Continuing Review Process* IRB Policy shall be followed.
3. For instances involving studies which do not have an expiration date (i.e., require continuing review) and have passed its annual check-in date, the procedures outlined in the *Continuing Review Process* IRB Policy shall be followed.

D. When the non-compliance is alleged in a clinical trial within the research community at Orlando Health, further information must be obtained to determine whether the allegation is true.
1. An investigative team will be convened by the CORO.
   a. Individuals alleging non-compliance may be in sensitive positions relative to colleagues and superiors and must be protected from possible retaliation.
   b. Investigations will be confidential and whistleblower protections, as well as researcher integrity, will be respected.
2. When a confirmed report of non-compliance is received, an initial inquiry should be made promptly to determine whether the non-compliance is serious or continuing.
3. The CORO Director or designee will immediately notify the IRB Chair (or designee about the report).

E. Reviewing reports of Major Protocol Deviations/Violations and/or Regulatory Non-compliance:
1. When a report of a Protocol Deviation or Non-Compliance is received, the Principal Investigator or other parties may be asked to provide additional information in order to ensure the report is complete.
2. The report will be reviewed by the IRB Office, IRB Chair or designee. If needed, the IRB Office and/or IRB Chair will investigate the incident with any combination of the following individuals: the CORO, Principal Investigator, Director of Research, and/or the institutional human subjects protection signatory official.
3. If needed, the IRB Chair will determine if an immediate, temporary suspension of participant enrollment is required for the project in question as well as for other projects with the same Principal Investigator in an effort to ensure the welfare of research subjects and to ensure compliance with applicable regulatory requirements. This initial decision will be based on preliminary information and the seriousness of the situation.
4. Final IRB determination:
   a. If the IRB Chair determines the non-compliance to be non-serious and/or non-continuing:
      1) The IRB will provide a written acknowledgement letter to the Principal Investigator in response to the report.
      2) If one exists, the temporary suspension of patient enrollment will be lifted.
   b. Otherwise, the IRB Chair or designee may decide to consult with the Board at a convened meeting for a determination.
      1) If this is the case, the IRB office will distribute the report at the next available Board meeting.

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2) In order to determine serious or continuing non-compliance, it may be necessary to require an audit of study records at which time the Principal Investigator will be required to produce all signed consent forms and all data related to the study project at the time of the audit.
3) If, at a convened meeting, the IRB determines the incident to indicate serious and/or continuing non-compliance, then the procedures outlined in the IRB Policy #0330-1019 "Study Closure, Termination, or Suspension of Research" will be followed.

5. The Principal Investigator will be informed in writing of the required actions and/or results of the IRB's review.
6. The IRB Office shall maintain documentation for all IRB decisions and audits.

V. DOCUMENTATION:

A. Major Protocol Violation/Deviation Form
B. Continuing Review Application for Human Research Minor Protocol Deviation Log Sheet

VI. REFERENCES:

A. IRB Policy #0330-1007: *Continuing Review Process*
B. IRB Policy #0330-1019: *Study Closure, Termination, or Suspension of Research*
C. Code of Federal Regulations – 21 CFR 56.108 (b) and 45 CFR 46.108 (4)
D. Guidance for Industry- E6 Good Clinical Practice (4.5)
E. IRB Forms and Templates

VII. ATTACHMENTS:

A. Major Protocol Deviations/Violations & Regulatory Non-Compliance Examples

Orlando Health Institutional Review Board

MAJOR PROTOCOL DEVIATIONS/VIOLATIONS & REGULATORY NON-COMPLIANCE EXAMPLES

A **protocol deviation** is defined as any change, divergence, or departure from the research protocol that is under the investigator's control and that has not been previously approved by the IRB. A **major protocol deviation/violation** is a protocol deviation that either potentially places the subject (or others) at a greater risk of harm (rights, well-being and/or welfare), potentially violates ethical principles, potentially has a major impact on the integrity of study data or the scientific design of the study, and/or resulted from willful or knowing misconduct on the part of the Investigator(s) or their study team. A **minor protocol deviation** is a protocol deviation that DOES NOT meet the definition of a major protocol deviation/violation.

Below are examples of major deviations/violations:

FAILURE TO PROPERLY DOCUMENT INFORMED CONSENT

- A completed consent form is missing from the research records
- Consent form is signed after the research participant started study assessments/treatments/interventions

FAILURE RELATED TO ELIGIBILITY OR TREATMENT ACCORDING TO PROTOCOL

- Participant did not meet all eligibility criteria as specified by the protocol
- Unable to verify eligibility because of the lack of source documentation
- An incorrect or additional agent/treatment/procedure was used which is not permitted by protocol
- Repetitive or systematic errors in dosing (error greater than +/- 10%)
- Dose modifications not followed per protocol or the modification was unjustified
- Repetitive or serious errors in timing or scheduling of doses/procedures

FAILURE TO ASSESS/REPORT ADVERSE EVENTS ACCORDING TO PROTOCOL

- Exams/tests necessary to assess toxicities were not performed per protocol
- Failure to report a toxicity that would require filing a serious or unexpected adverse event report per protocol

FAILURE TO EVALUATE TREATMENT RESPONSE ACCORDING TO THE PROTOCOL (FOR ONCOLOGY TRIALS)

- The initial site(s) of tumor involvement was inaccurately documented
- Tumor measurements/evaluation were not performed or were not documented adequately in order to assess baseline or to interpret any treatment response
- Protocol-directed response criteria not being followed
- The claimed response (e.g., Partial Response (PR), Complete Response (CR), etc.) cannot be verified

Regulatory Non-compliance is a failure to comply with any of the federal and/or state regulations or institutional policies governing human subjects research that may potentially compromise human subjects protection or the integrity of the Orlando Health IRB's human subjects protection program.

Below are examples of Regulatory Non-Compliance:

- Performing non-exempt human subjects research without first obtaining IRB approval
- Having a study lapse in its IRB approval (i.e., study expired)
- Study-specific manuals (e.g., MRI manuals, lab manuals, etc.) were not followed
- Failure to report a certain disease/condition to the local county health department as mandated by Florida State Statutes
- Consent form used for research participant(s) was not the most current IRB-approved stamped version
- Consent form does not include updates or information required by IRB
- Material failure of the Principal Investigator, including their study staff, to comply with regulations governing human subject protections.

NOTE: THIS IS NOT AN EXHAUSTIVE LIST