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Research: Protocol Deviations & Non-compliance- AD.0194

PURPOSE

The purpose of this policy is to describe the procedures for reporting and processing reports of protocol deviations submitted to the IRB. Our policies guide our practices and ensure that we place people at the heart of all we do to deliver the best outcomes and safest care.

APPLICABILITY

This policy applies to Lakeland Regional Health's **Workforce** and **Research Personnel** engaged in research.

POLICY

I. General

A. The approved study **protocol** is the equivalent of a contract between the IRB and the **Principal Investigator** (PI). PIs must follow the study protocol as the IRB has approved it. Adherence to the study protocol is important since non-compliance may lead to incorrect decisions affecting the safety or efficacy of the study procedures and may result in adverse consequences for patients. IRBs have the authority to sanction, suspend, or terminate approval if there has been serious or continuing non-compliance with the study as the IRB approved it.

B. PIs will conduct the trial in compliance with the protocol agreed to by the Sponsor, the appropriate regulatory authority(ies), if applicable, and as approved by the IRB.

C. Protocol deviations and reports of **non-compliance** may come from many sources. The PI may self-report non-compliance and is encouraged to do so. Self-reporting will be looked upon favorably during assignment of corrective actions. In other cases, a research subject may submit a complaint, a member of the research team may report an incident, or an incident may be discovered during IRB review or post-approval monitoring. Research staff who become aware of potential non-compliance

should notify the PI as soon as possible.

D. Instances discovered during IRB review or via post-approval monitoring are reported by IRB staff as indicated in this policy.

E. A PI may also be required to report incidents to his/her department or the study sponsor; PIs are responsible for knowing reporting requirements that may exist beyond those specified by the IRB and for following those requirements.

II. Major/Minor Protocol Deviations

A. For the purposes of determining the mechanism of review, deviations are classified as major or minor.

1. **Major deviations** or violations require review at a convened meeting of the IRB.
2. **Minor deviations** or violations can be resolved by IRB staff and do not require submission to the full convened IRB.
3. Due to the wide variability of research protocols, the PI will make the determination if the deviation is major or minor and submit accordingly. If there is a question about whether the deviation is major or minor, contact the IRB Administrator.
    a. The IRB Office has the authority to change the severity of the deviation once a review is conducted, if necessary.
    b. Best practice is to submit both major and minor protocol deviations in IRBNet immediately upon notification or discovery.

B. The PI should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval from the IRB of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).

1. The PI may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval. In these instances, this deviation must be submitted to the IRB within ten (10) business days.

C. The PI or person designated by the PI, should document and explain any deviation from the approved protocol.

D. The IRB Administrator will screen all notices of protocol deviations using a checklist.

E. Major protocol deviations

1. Any change, divergence, or departure from the study design or procedures of a research protocol that the IRB has not approved and that affects the subject's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data constitutes a major protocol deviation. The PI is responsible for reporting major protocol deviations to the IRB.
2. Upon discovery, the PI must submit all major protocol deviations to the IRB

in writing within ten (10) business days along with any applicable attachments. Notification does not preclude additional investigation or inquiry by the IRB. The PI also reports all protocol deviations to the sponsor, if applicable, following the sponsor's requirements.

F. Minor protocol deviations

1. Changes or alterations in the conduct of the trial which do not have a significant impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data are considered **minor protocol deviations**.
2. All instances of minor protocol deviations or non-compliance must be promptly reported via IRBNet.

III. Non-Urgent, Non-Emergent Protocol Deviations/Exceptions

A. A protocol exception is a type of planned change to the research for a single subject. Unlike an amendment, a protocol exception is not a permanent revision to the research protocol. IRB approval of a protocol exception must occur prior to its implementation with the exception of the use of a short form consent document.

B. The PI is responsible for submitting any protocol exception requests. Failure to submit protocol exception requests represents non-compliance with the federal regulations, LRH policies and determinations of the LRH IRB.

C. If the PI anticipates that there will be future requests for the same deviation, then the protocol should be amended.

D. If the research involves an investigational agent (drug, device, or biologic), prior approval by the sponsor is also required.

E. When the research involves an investigational device and the changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of the subjects, FDA pre-approval is required (21 CFR 812.150(a)(4)).

PROCEDURE

I. Informal Resolution for Specified Minor Non-compliance or Minor Protocol Deviations

A. In addition to minor protocol deviations, one-time or isolated cases of the following types of incidents constitute **minor non-compliance** and can be resolved by the IRB:

1. Over-enrollment in a minimal risk, non-exempt study.
2. Unapproved changes to personnel, other than the PI or supervising investigator, when:
    a. Any new personnel have completed required human subjects protection training before being involved in human subjects research activities, or
    b. Removal of personnel does not adversely affect the qualifications of the research team or its ability to safely carry out the research.

3. Unapproved changes in the type of compensation (e.g., changing from cash to gift cards), when the change does not alter:
    a. The amount of compensation; and
    b. Plans for pro-rating compensation; and
    c. Privacy or confidentiality provisions (e.g., no changes to the collection of identifiers, whether identifiers are connected to data, etc.).

B. The IRB Administrator assesses the totality of the circumstances regarding the incident. If it is determined that the incident is eligible for informal resolution, it is handled as follows:
    1. Verify the incident is a one-time or isolated case by checking IRB records. Repeated incidents associated with a PI or project may constitute **continuing non-compliance**, and are not eligible for informal resolution.
    2. Rectify the issue by advising the PI to:
        a. Promptly obtain IRB approval by submitting an amendment to the protocol if they have not already done so; a reasonable deadline for completing this step should be established if appropriate; and
        b. Adhere to the approved protocol until the amendment to the protocol receives IRB approval (if appropriate).
    3. Educate the PI and research coordinator by informing them of the minor non-compliance and reminding them that IRB approval must be obtained for any changes prior to implementation.
    4. Document the incident as a minor non-compliance event in IRBNet. Documentation supports identification of patterns of non-compliance.
    5. Minor instances of non-compliance and minor protocol deviations will be administratively reviewed in IRBNet and reported to the IRB as information items.

C. The incident will be forwarded for review in accordance with the major protocol deviation review process if:
    1. IRB staff determine the incident is not appropriate for informal resolution; or
    2. The PI does not address the issue within a reasonable time frame.

II. IRB Review of Major Protocol Deviations and Non-compliance

A. Upon receipt of a report of potential non-compliance or a major protocol deviation, the IRB Administrator will forward the information to the IRB Chair.

B. In cases involving serious harm to subjects or where immediate action is needed to prevent such harm, the AVP of Research & Sponsored Studies and the Institutional Official (IO) should also be informed.

C. The PI will submit a report summarizing the incident(s) and outcome(s), which is

provided to the convened IRB for review.

D. If the facts of the case raise serious concerns about the rights, safety, or welfare of participants, the IRB may suspend approval of the research while the case is under review.

E. After the review, the IRB issues a formal determination of the type of non-compliance (i.e., serious and/or continuing). If the IRB determines that neither serious nor continuing non-compliance has occurred, the IRB may dismiss the allegations or determine the non-compliance is minor and delegate handling of corrective actions to the IRB Administrator.

F. If the IRB determines that serious and/or continuing non-compliance has occurred, the IRB:

    1. Notifies the PI of the serious and/or continuing non-compliance determination and documents the decision and communication to the PI within the IRB electronic system;
    2. Reports the serious and/or continuing non-compliance to the IO, and to Federal agencies (e.g. FDA or OHRP) when required, and to any Federal agency that provides funding support for the research project;
    3. Determines whether a study modification is required to address newly-identified risks.
    4. May also require additional actions such as, but not limited to:
        a. Providing a warning or reminder to the PI with instructions on how to avoid future incidents, clarifications regarding requirements and rules, etc.;
        b. Requiring additional human subjects protection training for the PI/research team;
        c. Requiring the PI to submit a corrective action plan;
        d. Recommending that the IO (or designee) work with the appropriate physician leader(s) and AVP of Research & Sponsored Studies to determine appropriate actions regarding the data collected as a result of the non-compliant actions;
        e. Restricting the ability to serve as PI on human subjects protocols (e.g., requiring a supervising co-PI, barring future eligibility as PI, etc.);
        f. Suspension of the research;
        g. Termination of the research;
        h. Notification of current subjects (required when such information might relate to subjects' willingness to continue to take part in the research);
        i. Additional information provided to subjects who have completed study procedures;
        j. Modification of the research study;

k. Modification of the information disclosed during the consent process;

l. Re-consenting of current subjects;

m. Monitoring of the research;

n. Monitoring of the consent process; or

o. Shortening of the continuing review cycle.

G. The IRB may refer the issue to other organizational entities, such as legal counsel, risk management, compliance, etc., in addition to the recommended corrective actions.

H. PIs are encouraged to play an active role in the non-compliance review process. The PI is provided with an opportunity to review and comment on non-compliance reports provided to the IRB for consideration. PI comments must be received by the deadline established by the IRB Administrator to be included with information provided to the IRB. The PI will be invited to address the IRB during the meeting where the non-compliance review occurs. A report summarizing the IRB's determinations and recommended corrective actions will be provided to the PI for review and comment prior to submission to the IO for consideration of corrective actions. Comments must be provided by the deadline established by the IRB Administrator. The PI's comments will be forwarded to the IRB for reconsideration if the comments reveal new factual information or other circumstances that are reasonably likely to affect the IRB's determinations or recommendations.

III. **Institutional Official Review**

In cases of serious or continuing non-compliance, the IO receives a final report documenting the non-compliance review process, the IRB's recommendations, and any response to these recommendations by the PI. The IO may accept, revise, add to, or reject any or all of the IRB's recommended corrective actions but may not change the IRB's determinations related to the level of non-compliance or overturn the IRB's decision to suspend or terminate IRB approval, to require modifications to the approved protocol, or to require more frequent or higher-level IRB review. The final report documenting the Institutional Official's actions is provided to the PI, the appropriate physician leader(s), the AVP of Research & Sponsored Studies, the IRB Chair(s), and for the IRB files.

IV. **Follow-Up**

A. PIs are responsible for ensuring the corrective actions outlined in the final non-compliance report are implemented by the time-frames established in the report. Failure to meet the conditions established in the report will result in additional review by the IRB and possible termination or suspension of IRB approval.

B. Progress reports must be provided to the IRB in the time frame outlined in the corrective action(s).

V. External Reporting

When applicable, incidents of serious or continuing non-compliance must be reported to the

Office of Human Research Protections per the requirements set forth in 45 CFR § 46.108(4)(i) and the funding agency or sponsor in accordance with their requirements. Similarly, reports of serious or continuing non-compliance must be provided to the Food and Drug Administration for FDA-regulated research in accordance with 21 CFR § 56.108(b), 21 CFR § 56.113, 21 CFR § 812.150. When appropriate, preliminary reports may be filed pending final resolution of the case.

DEFINITIONS

I. **Continuing non-compliance**: Repeated acts of non-compliance in the conduct of human subjects research suggesting a pattern indicative of a lack of understanding or attention to adequate safeguarding of the rights, safety, or welfare of human subjects or of university policies and/or non-university regulatory requirements for the conduct of human subjects research. Continuing non-compliance is characterized by the frequency rather than the magnitude of the non-compliance. Examples of continuing non-compliance include, but are not limited to:

   i. Repeated failure to obtain IRB approval prior to initiating human subjects research activities;

   ii. Continuing to engage in non-compliant activities after being notified or advised of concerns;

   iii. Recurring late submissions of continuing review applications resulting in repeated lapses in approval;

   iv. Multiple instances of serious or minor non-compliance; this includes multiple incidents within a single project or multiple incidents by a single investigator across more than one project; or

   v. Failure to respond to incidents of non-compliance or failure to enact required corrective actions.

II. **Exempted protocol**: The information included in the final IRB application upon which a determination of exemption was granted, including any attachments, addenda or appendices, and subsequent amendments for modification or status check submissions.

III. **Major Protocol Deviations**: Any change, divergence, or departure from the study design or procedures of a research protocol that the IRB has not approved and that affects the subject's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data.

IV. **Minor non-compliance**: Non-compliance that does not rise to the level of serious or continuing non-compliance. Minor non-compliance typically involves administrative oversights, non-substantive unapproved changes, etc. Non-compliance that does, or reasonably may, adversely affect the rights, safety, or welfare of research subjects is not minor, even if no actual harm has occurred. Examples that may be deemed minor include, but are not limited to:

   A. Implementing non-substantive changes to approved procedures without IRB approval, such as:

      1. Re-wording survey or interview questions where the meaning and scope of the question does not change;

      2. Wording changes in recruitment materials or consent forms that do not

change the meaning of the information provided or result in excluding any required element(s) of consent;

3. Changing the order in which study conditions are administered, as long as a specific order is not necessary to minimize risk;
4. Enrolling subjects who do not meet the inclusion or exclusion criteria, except in the circumstances described as serious non-compliance below;
5. Exceeding the approved number of subjects in a study; or
6. Unapproved changes in study personnel, when the changes do not alter the qualifications of the overall research team and all personnel have completed required human subjects protection training.

V. **Minor Protocol Deviation**: Changes or alterations in the conduct of the trial which do not have a significant impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

VI. **Non-compliance**: Any action or activity associated with the conduct or oversight of human subjects research that fails to comply with either the IRB-approved research plan, or federal regulations or institutional policies governing human subject research. Non-compliance can result from action or omission, and may be minor, serious, and/or continuing as defined below:

A. In general, intentional deviations from the approved protocol constitute non-compliance, unless enacted to eliminate apparent immediate hazards or risks to research subjects.

B. Unintentional or unavoidable deviations that are outside of the reasonable control of the researcher(s) do not constitute non-compliance. For example:

1. A subject cannot attend an appointment which results in a change in timing of study procedures (when the change does not adversely affect risk to subjects);
2. An ineligible subject is enrolled in the study due to misinformation provided to the researcher; or
3. Exceeding the number of subjects in a study in limited circumstances when enrollment is outside the control of the researcher, (e.g., responses to a recruitment flyer with a link to an online survey exceed the number expected; in this case, the researcher cannot control who sees the flyer, how many individuals choose to respond, etc.).

VII. **Principal investigator (PI)**: The individual ultimately responsible for the conduct of human subjects research, including oversight of investigators serving on a research team.

VIII. **Protocol or approved protocol**: The information included in the approved IRB application, including any attachments, addenda, or appendices. Information approved in subsequent amendments (e.g., modification, continuing review, closure) or status check submissions are included in this definition.

IX. **Researchers/Research Personnel:** All individuals designing or directing research, serving as a principal or co-investigator, enrolling research subjects (including obtaining subjects' informed consent or screening potential subjects), or making decisions related to eligibility to

participate in research, analyzing or reporting research data, analyzing or reporting adverse events, or submitting manuscripts concerning the research publication.

X. **Serious non-compliance**: Non-compliance that compromises the safeguarding of the rights, safety or welfare of human research subjects, or that does or may reasonably adversely affect the rights, safety, or welfare of human research subjects, even if no actual harm occurred. Acts that are determined by the IRB to be flagrant or intentional violations of IRB requirements may also constitute serious non-compliance. The IRB will consider the circumstances surrounding the case when making a decision related to serious non-compliance. In general, examples of serious non-compliance include, but are not limited to:

    i. Failure to obtain IRB approval or determination of exemption prior to initiating research activities with human subjects;

    ii. Allowing unqualified or untrained individuals to perform research procedures or monitor subject safety;

    iii. Failure to obtain informed consent or failure to provide participants with all information necessary to constitute meaningful informed consent unless a waiver has been previously granted by the IRB;

    iv. Enrolling a child in a research study without the informed consent of a parent or legal guardian unless parental consent was previously waived by the IRB;

    v. Enrolling subjects from a vulnerable population (i.e., children, prisoners, cognitively impaired individuals, subordinates, etc.) when their inclusion is not described in the IRB-approved protocol and appropriate protections are not in place;

    vi. Enrolling subjects who do not meet the approved eligibility criteria when doing so compromises the safety or well-being of the subjects;

    vii. Failure to follow approved measures for protecting privacy and confidentiality when the failure presents any risk of harm to the research subject (such as harm to their reputation, social or psychological harm, risks of legal or civil liability, embarrassment, harm to workplace or family relationships, etc.);

    viii. Implementing unapproved changes to research activities that increase risks to participants or adversely affect their rights, safety, or welfare (e.g., adding survey questions that collect sensitive information, substantially increasing the duration or intensity of exercise activities, adding plans to collect data from private records without subject consent, changes to confidentiality protections, etc.);

    ix. Failure to report serious adverse events or unanticipated problems involving risks to subjects or others as required by IRB policy;

    x. Instructing or knowingly allowing subordinates (e.g., research assistants, employees, students, etc.) to engage in activities that are contrary to IRB or institutional policies or regulatory requirements;

    xi. Providing false or intentionally misleading information to the IRB; or

    xii. Multiple issues suggesting a lack of oversight, inaction, or negligence such that research subjects' rights, safety, or welfare could be adversely affected.

XI. **Workforce**: All LRH employees, volunteers, trainees/students, contractors, and Medical Staff.

REFERENCES

I. Iowa State University - Protocol Deviation Non-compliance
II. Mayo Clinic Research - Submitting Reportable Events to the IRB
III. Elligo SOP.510 – Protocol Deviations
IV. 45 CFR 46.108
V. 21 CFR 56.108
VI. 21 CFR 812.150

Approval Signatures

Step Description	Approver	Date
	Danielle Drummond: 0001 President & Chief Executive Officer - LRHS	03/2024
	Jonn Hoppe: 1011 Executive VP, Chief Legal Officer-General Cou	03/2024
	Timothy Regan: 0009 President - LRMC/Chief Medical Officer	03/2024
	Renee Reed: 4064 Senior Attorney	03/2024
	Deana Nelson: 4080 SVP - Administration and Corporate Initiative	03/2024
	Georgia Ann Keriazes: 0729 QI/ Due Pharmacist	03/2024
	Andrew Bugajski: 4387 AVP - Research and Sponsored Studies	12/2023