***Noncompliance in Clinical Trials***

1. **PURPOSE**

This Standard Practice Guideline (SPG) describes the procedures, processes, and responsibilities for communicating, documenting, and reporting clinical research noncompliance and escalating cases of noncompliance for clinical trials.

(**MANDATORY LANGUAGE**)

1. **SCOPE**

This SPG applies to all research staff including sponsors and monitors involved in the conduct and management of clinical trials and their interactions with associated clinical research participants.

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*[Optional: Insert any additional details necessary to further define the scope of this SPG]*

1. **POLICY**

**Good Clinical Practice (ICH GCP)**

This SPG aligns with the Good Clinical Practice (ICH GCP) guidelines established by the International Council on Harmonization (ICH). Section 4.5.3 states *The investigator, or person designated by the investigator, should document, and explain any deviation from the approved protocol.*

In addition, Section 5.20.1 stipulates *noncompliance with the protocol, SOPs, GCP, and/or applicable regulatory requirement(s) by an investigator/institution, or by a member(s) of the sponsor’s staff should lead to prompt action by the sponsor to secure compliance.*

Finally, ICH Section 5.20.2 makes note of actions to be taken for serious and/or persistent noncompliance, indicating *If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the investigator’s/institution’s participation in the trial.*

**FDA Regulation(s)** (if applicable)

21 CFR 56.108(b) requires that the IRB shall follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Food and Drug Administration of:

1. Any unanticipated problems involving risks to human subjects or others;
2. Any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB; or
3. Any suspension or termination of IRB approval.

**University of Michigan Office of Human Research Participant Protection (HRPP)**

*The HRPP promotes an organizational culture that encourages a commitment to compliance with the legal, regulatory, and ethical principles that govern human subjects research. The program relies on a system of self-regulation and integrated oversight to accomplish this objective and reflects an emphasis on the high ethical standards and values demanded of the most outstanding research institutions.*

*Generally, allegations of potential noncompliance related to specific research projects are first reviewed by the responsible IRB. IRBs may take interim actions as noted in their SOPs - including suspension of research - to protect human subjects while a concern is under review.*

**Additional Regulations or Policies** [ ]  **N/A**

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*[Optional: Insert any additional project, department, sponsor, institution, state, or federal policies that apply]*

1. **DEFINITIONS**

COMPLIANCE: In relation to research: Adherence to all relevant trial-related requirements, ICH Good Clinical Practice (ICH GCP) requirements, and the applicable institutional, state, and federal regulatory requirements. (IRB definition)

CONTINUING NONCOMPLIANCE: Non-compliance (serious or non-serious) that has been previously reported, or a pattern of ongoing activities that indicate a lack of understanding of human subjects protection requirements that may affect research participants or the validity of the research and suggest the potential for future noncompliance without intervention. Examples of continuing non-compliance may include but are not limited to: repeated failures to provide or review progress reports resulting in lapses of IRB approval, inadequate oversight of ongoing research, or failure to respond to or resolve previous allegations or findings of noncompliance. (IRB definition)

INTERNATIONAL COUNCIL ON HARMONISATION (ICH): A joint initiative involving both regulators and research-based industry representatives of the European Union, Japan, and the USA in scientific and technical discussions of the testing procedures required to assess and ensure the safety, quality, and efficacy of medicines

NONCOMPLIANCE: Non-compliance that has the potential to increase risk to research participants, compromise participants’ rights or welfare, or affect the integrity of the research/data or the human subjects protection program. Examples of serious noncompliance may include, but are not limited to: conducting or continuing non-exempt human subjects research without IRB approval; lack of legally effective informed consent from research participants; failure to report or review serious adverse events, unanticipated problems, or substantive changes in research; or inappropriate oversight of the research to insure the safety of human subjects and the integrity of the research/data. (IRB definition)

**OFFICE OF RESEARCH COMPLIANCE REVIEW** (ORCR): provides objective analysis and evaluation of non-financial research activity compliance for investigator-led research studies, with emphasis on human subjects studies, units of U-M's [Human Research Protection Program (HRPP)](https://research-compliance.umich.edu/human-subjects) and of the HRPP as a whole.

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*[Optional: Insert any additional definitions for technical or special terms used within the Standard Practice Guideline that may not be familiar to the lay reader]*

**Note:** Some of the definitions above were obtained from the IRBMed Glossary. These definitions were current as of 01-Oct-2022 and are subject to change. Please see the [IRBMed Glossary](https://research.medicine.umich.edu/office-research/institutional-review-boards-irbmed/guidance/glossary) for the most current definitions and additional guidance.

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1. **ROLES AND RESPONSIBILITIES**

**Principal Investigator**

An individual filling the role of Principal Investigator (PI) is ultimately *responsible* for the following activities:

* Understands and adheres to the research protocol, regulatory, institutional, and when applicable, ICH Good Clinical Practice (ICH GCP) guidelines that define compliance and non-compliance
* Manages and oversees the conduct of clinical trials, including the documentation and reporting of noncompliance to oversight and/or regulatory bodies, as appropriate
* Creates processes and procedures to document non-compliance
* Communicates with the IRBMED, ORCR and other applicable entities in the case of noncompliance
* Responds to any reports of noncompliance made by study staff, monitors, auditors, Co-Investigators, vendors, sponsors, or research subjects
* Educates study staff and research subjects to prevent continuing non-compliance
* Oversees the termination of a clinical research site or the clinical trial for reasons of continuing noncompliance, when appropriate
* Delegates responsibilities where appropriate

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*[Optional: Insert any additional details regarding the responsibilities of the Principal Investigator*]

**Study Coordinator(s)/Designee**

An individual filling this role may be responsible for the following activities:

* Understands and adheres to the research protocol, regulatory, institutional, and when applicable, ICH Good Clinical Practice (ICH GCP) guidelines that define compliance and non-compliance
* Documents noncompliance in an accurate and time-sensitive manner
* Reports identified noncompliance to the PI
* Seeks to minimize the re-occurrence of protocol deviations and other sources of non-compliance through process improvements, additional training, etc.

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*[Optional: Insert any additional details regarding the responsibilities of the Study Coordinator/Designee*]

**Additional Roles and Responsibilities** [ ]  **N/A**

**(MANDATORY LANGUAGE)**

*[Optional: Insert any additional role(s) and responsibilities that apply to this SPG]*

1. **PROCEDURE**

**Protocol Noncompliance**

*[Describe the process for communicating, documenting, and reporting identified protocol noncompliance. This may include processes for (re)education of study staff and participants, completion of protocol deviation records, and reporting to Sponsor, IRB and/or other oversight committees.]*

**Standard Practice Guideline (SPG) Noncompliance**

*[Describe the process for communicating, documenting, and reporting identified noncompliance with site SPGs. This may include processes for (re)education of staff, completion of a corrective action plan, and/or amending current SPGs.]*

**Regulatory Noncompliance**

*[Describe the process for communicating, documenting, and reporting identified regulatory noncompliance. This may include processes for (re)education of study staff and participants, completion of protocol deviation records, and reporting to Sponsor, IRB and/or other oversight committees.]*

**Escalation of Identified Noncompliance Issues**

*[Describe the process for escalating identified continuing noncompliance and serious noncompliance. This may include documentation, remediation, and reporting, to the appropriate study team member, regulatory bodies, etc.]*

**Additional Procedures** [ ]  **N/A**

*[Optional: Insert any additional relevant procedures. Provide enough detail to ensure the procedure is consistently carried out, without providing so much detail that violations occur due to normal or expected variations in the work.]*

1. **REFERENCES**

FDA -Title 21 Subpart C - IRB Functions and Operations:

<http://www.ecfr.gov/cgi-bin/retrieveECFR?gp=1&SID=5b79c575275c2aa91f15b79964501546&ty=HTML&h=L&mc=true&n=sp21.1.56.c&r=SUBPART>

FDA Title 21 CFR 56.108 - IRB functions and operations:

<http://www.ecfr.gov/cgi-bin/text-idx?SID=d0bff1ef1c16aec48c8637520a7c5fa3&mc=true&node=se21.1.56_1108&rgn=div8>

International Council on Harmonisation (ICH):

<http://www.ich.org/>

<https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf>

University of Michigan - Office of Research Compliance Review (ORCR):

<http://research-compliance.umich.edu/office-human-research-compliance-review-ohrcr>

University of Michigan - Operations Manual - Quality Assurance and Research Compliance:

<http://research-compliance.umich.edu/operations-manual-quality-assurance-and-research-compliance>

University of Michigan - Policy Statement on the Integrity of Scholarship and Procedures for Investigating Allegations of Misconduct in the Pursuit of Scholarship and Research:

<http://spg.umich.edu/policy/303.03>

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*[Optional: Insert any additional SPG references]*

1. **APPENDICES**

(**MANDATORY LANGUAGE**)

*[Optional: Insert any additional SPG appendices]*