**GUIDANCE: Protocol Deviations**

**Policy:** It is the policy of UTHSC-H that research must be conducted in compliance with the protocol, institutional policies and procedures and applicable regulations. Changes in approved research, during the period for which CPHS approval has already been given, may not be initiated without CPHS review and approval except when necessary to eliminate apparent immediate hazards to the subject. The Principal Investigator must submit and receive approval from the CPHS before initiating any changes to a research study. (*from CPHS Policy Change Requests and Protocol Amendments*)

**Key Terms:**

**Protocol Deviation:** Any departure from the protocol without prior CPHS approval is a protocol deviation. In this context the term protocol includes all the documents approved by CPHS, institutional policies and procedures and applicable regulations. At this institution, protocol deviation and protocol violation are used interchangeably.

**Major Protocol Deviations:** A deviation that affects safety of subjects is regarded as a major protocol deviation.

**Minor Protocol Deviation:** A deviation that does not affect the safety of subjects is regarded as a minor protocol deviation.

**Identification:** Deviations from the protocol may be identified by several mechanisms:

* research team
* research team appointed monitors
* sponsor monitors
* CPHS monitors
* CPHS staff
* federal inspections

**Assessment by PI:** When a protocol deviation is discovered, it is the Principal Investigator’s responsibility to assess whether a protocol deviation meets the definition of major or minor protocol deviation.

In general, non compliance on the part of the research subject is not considered a protocol deviation. For example, if a research subject misses a study visit or comes for the visit outside the visit window. These may not meet the definition of major protocol deviations. However, if the non compliance amongst research subjects is widespread the research team should consider strategies to improve compliance. For example, if many research subjects are not compliant in taking the study drug, the research team should investigate to see if this is because of unpleasant side effects and try to address the problem. If several research subjects miss their appointments, the research team might institute a system to remind subjects about their upcoming appointment by calling them a day or two before the appointment to confirm. The proposed solution should be submitted to the CPHS for review and approval prior to implementation.

The decision on whether a protocol deviation is major or minor often depends on the particular research study. For example, missing a laboratory test on a sample collection protocol might not be as serious a risk for the subject as missing a safety laboratory test on an early phase clinical trial.

When there is a change in staff, the new research staff may discover protocol deviations while reviewing study documentation. The Principal Investigator should review each deviation to determine if it is a major or minor deviation. A deviation that would have been major at the time of occurrence might be minor at the time it is detected.

After a regular monitoring visit, usually towards the beginning of the research, the monitor might uncover several protocol deviations. The Principal Investigator should review each deviation and report all the deviations that meet the definition of a major deviation. If there is more than one major deviation, these may be reported to the CPHS using a single protocol deviation form with a clear corrective action plan.

**Reporting:** Major protocol deviations must be submitted to the CPHS within 7 days of first knowledge of the investigator as per CPHS policy “Unanticipated Problems Involving Risks to Subjects or Others”, using the Protocol Deviation form via iRIS. The form should contain adequate information about the protocol including;

* Detailed narrative describing the deviation, how the deviation was discovered, the risks the subjects were exposed to and the measures taken to minimize risk.
* A detailed corrective action plan to prevent similar deviations in the future. This may involve one or more strategies such as:
  + Training research team. Some methods for training include:
    - Requiring the research team members to take additional training GCP modules,
    - Working with Clinical Trials Resource Center to organize a training session on GCP for research team,
    - Requesting the study monitor (for industry sponsored studies) to conduct a training session on the protocol and protocol related procedures.
    - In-service to clinical teams assisting with the research.
  + Protocol amendment to avoid similar deviations.
  + Re-consenting research subjects.
  + Terminating the participation of the affected research subjects from the research study.
  + Exclusion of the data of affected research subjects from analysis,
  + Planned monitoring or audit of the research after implementing corrective action plan.

The research team should log minor protocol deviations in a protocol deviation log. Protocol deviation logs should be submitted at the time of continuing review. Research teams should review the protocol deviation logs periodically and determine if the deviations indicate a larger systemic problem with the implementation of the research. Appropriate corrective measures should be taken to rectify any systemic problems.

For industry sponsored research, the Principal Investigator should follow the sponsor policy for reporting protocol deviations to the sponsor or CRO. This is different from the reporting requirements to CPHS. Sponsor monitors sometimes insist that all identified protocol deviations be reported to CPHS. Directing the monitor to this institutional guidance on reporting protocol deviations might help.

**Avoiding Common Deviations**: According to the protocol deviations submitted to CPHS in the past months, some of the most common deviations are use of unstamped or wrong version of consent or HIPAA document, use of unapproved recruitment strategies, and missed study procedures.

* A strong quality management program including regular review of regulatory binder, consent documents and source documents.
* Good communication between all the members of the research team helps to reduce deviations. Some research teams find regular research meetings helpful.
* Training or in-service on protocol or study procedures for relevant staff.
* All relevant research team members should be updated on changes to the protocol and should have access to CPHS approved current documents, e.g. correct version of the consent documents and HIPAA documents.

# Applicable Regulations and Guidance Documents

* 45 CFR 46.103(b)(4)
* 21 CFR 56.108(a)(4)
* 21 CFR 312.30(b)
* ICH GCP 3.3.8; 4.5

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# Applicable Institutional Policies and Procedures

* CPHS Policy and Procedure – *Change Requests and Protocol Deviations*

# Attachments

* Protocol Deviation Log
* Protocol Deviation Form *(from iRIS)*

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