



Manual of Procedures

Section 16. Protocol Deviations

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16. Protocol Deviation

16.1 Definition

The term protocol deviation is not defined by the DHHS or FDA human subject regulations (45 CFR 46, 21 CFR 50). For the purpose of D2d, a protocol deviation is a departure from the protocol procedures. Deviations may vary from minor or major. Protocol deviations should be avoided.

Major Deviation may place participants at added risk or result in data that cannot be analyzed. Examples include:

- Randomization of a participant that did not meet the eligibility criteria.
- Study pills were not discontinued when a participant met a safety signal (e.g., calcium level > 1 mg/dl than the local upper limit of normal).
- A timed blood sample drawn outside of the window (e.g., the 120 minute glucose measured at 140 minutes after the glucose load).

Minor deviations may not place participants at added risk; however, many minor deviations cumulatively have a negative impact on the study. Examples include:

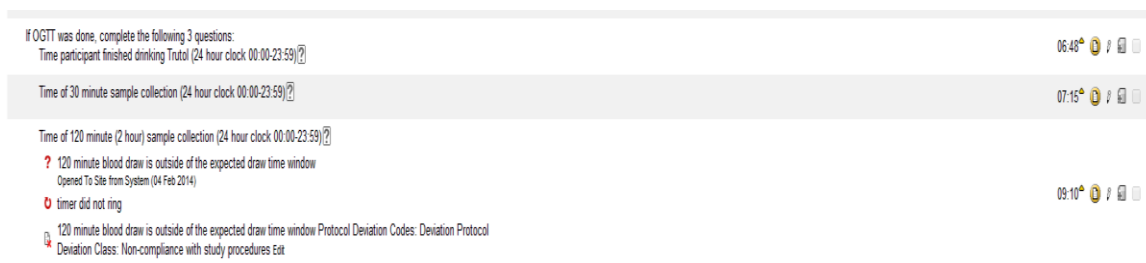
- A timed blood sample drawn just outside of the window (e.g., the 120 minute glucose measured at 128 minutes after the glucose load).
- A study visit occurring one week outside of the window.

16.2 Documentation

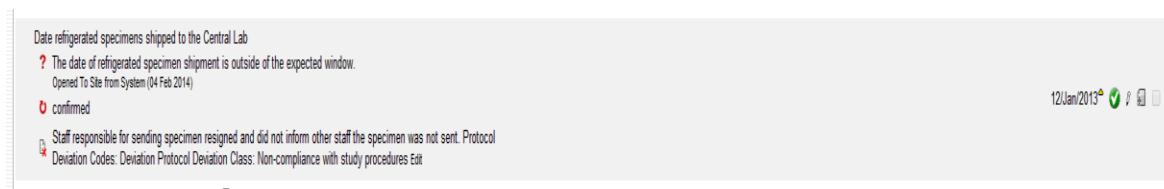
Protocol deviations are documented in EDC automatically (by the system) or manually (by the research staff).

- An automatic deviation is recorded by the system if data entered meet the criteria for a protocol deviation.
- A manual deviation is entered into the system by a user, either at the site or at the CC.

The following is an example of an automatically entered deviation that was recorded when a timed blood sample was drawn outside of the window.



The following is an example of a manually documented deviation that was entered by the research coordinator after discovering that refrigerated blood specimens were not sent to the Central Laboratory within the defined time period.



Please contact the CC for directions on the manual entry of protocol deviations.

Each protocol deviation is coded into one of the following categories for reporting to the Data Safety Monitoring Board (DSMB).

- Study pills not taken per protocol
- Non-compliance with visit schedule
- Use of a restricted medication
- Non-compliance with study procedures
- Randomization error
- Inclusion\Exclusion criteria not met
- Other

16.3 Monitoring

The CC monitors the number and significance of protocol deviations at each site. Sites may be asked to document and implement remediation plans to resolve any underlying issues that resulted in the occurrence of a deviation(s) and to prevent future ones. The remediation plan will be submitted to the CC for review.

The DSMB will be provided with a listing of all deviations and the sites at which they occurred with each report.

Sites will also need to follow local IRB policies for the IRB reporting of deviations.