



Exceptions and Deviations

Policy

- Federal regulations require that all protocol modifications (*any* change from the approved protocol) must be submitted to the IRB for review, and receive approval prior to implementation unless the change is to eliminate an immediate harm to a research subject. Most of these changes are submitted as amendments which undergo expedited or full committee review (see policy on *Amendments*)
- When an investigator anticipates a one time **significant**, time sensitive, intentional action or process that departs from an IRB approved protocol, he or she may request that a one time **exception** be granted by the IRB.
- Modifications that are noted or recognized after they occur are referred to as **deviations**. These changes may be classified as **significant or minor deviations**.
- Significant deviations/exceptions are events that actually or have the potential to
 - impact subject safety, welfare or rights
 - alter the risks or the benefits to the subject in a more significant, serious or negative way
 - impact the integrity of the data
 - effect a subject's willingness to participate

It is important to note that although a deviation/exception may not fit within one of the above categories, the fact that it had the potential to result in a negative outcome classifies the event as significant. Investigators will need to use their discretion when making this determination.

- Significant deviations must be reported to the IRB within 72 hours of their recognition through the unanticipated event process.
- Minor deviations/exceptions are deviations/exceptions that do not meet these criteria, must be tracked by the investigator and reported as applicable to the sponsor, FDA and through the data and safety monitoring process. Minor deviations and exceptions should also be reported to the IRB as part of the continuing review application.
- The IRB will make a determination for all significant deviations that are submitted whether they constitute serious or continuing noncompliance or an unexpected problem that creates potential or actual risks to subjects. Need for regulatory reporting is detailed in the "*Reporting*" policy.

Purpose

To distinguish and define, **Exceptions**, and **Deviations** and the associated policies and procedures.*

Definitions

Protocol Amendment

A *permanent, intentional* action or process that revises/amends a previously approved research protocol. There is a documented approval from the IRB, Sponsor, Data Safety Monitoring Board or Study Coordinating Center. The IRB has a form investigators may use to submit amendments for review and approval. Once approved, no further IRB follow-up is required. A separate policy addresses amendments (see policy on Amendments).

Protocol Exception

A *one time, intentional, time sensitive* action or process that departs from the IRB approved study protocol, intended for one occurrence. If the impact on the protocol and/or human subjects is deemed *significant*, prior documented IRB approval is required. If the impact on the protocol and/or human subjects is deemed *minor*, a report of the exception should be submitted to the IRB with the next continuing renewal.

Protocol Deviation

A *one time, unintentional* action or process that departs from the IRB approved study protocol, involving one incident and identified retrospectively (after the event). If the impact on the protocol is deemed *significant*, the deviation must be reported to the IRB within 72 hours. If the impact on the protocol is deemed *minor*, a report of the deviation should be submitted to the IRB with the next continuing renewal.

Minor vs. Significant Exceptions or Deviations

Protocol Deviations and Exceptions are classified as either *Minor* or *Significant*, based on both the actual direct or potential effect of the action or process on the specific subject(s), the entire subject population, and/or the overall integrity of the study design and results. While examples of each type will be provided, it is ultimately the PI's responsibility to determine whether the protocol deviation or exception is Minor or Significant, based on the following definitions.

Significant Deviation or Exception meets at least one of the following criteria:
Events that actually or potentially

- i) impact subject safety, welfare or rights
- ii) alter the risks or the benefit to the subject in a more significant, serious or negative way
- iii) impact the integrity of the data
- iv) effect a subject's willingness to participate

* Reference Appendix A: Elements and Characteristics Used to Define Protocol Modifications

Protocol Deviation Documentation and IRB Reporting

Once a protocol deviation is identified, it should be promptly reviewed and assessed by the PI and documented in the study records. The PI must make and include a determination as to whether the deviation's impact on the study is Minor or Significant.

It is up to the PI and research staff to determine a suitable method of documentation, such as a summary log, or a note to be filed in the investigator's study records. Whatever method is determined, it must include the following information:

- Date Deviation Occurred
- Date Deviation Identified
- Name of Research Staff that identified the deviation
- Description of Deviation
- Explanation why Deviation Occurred
- Corrective actions taken/Preventative measures implemented
- PI assessment whether Minor or Significant, and reason for choice
- PI signature and date

If the PI determines the deviation is minor as specified above, no further action is required to meet IRB reporting requirements. File documentation and submit copies at the next continuing renewal. If the PI determines the deviation is significant as specified above, the PI must submit to the IRB within 72 hours of identification. The "*Unanticipated Problem or Event*" form should be used. Report the deviation to the sponsor, FDA and DSMB as appropriate.

The IRB will review the report. As part of the review they will determine whether the deviation meets the criteria for regulatory reporting to OHRP, FDA or the sponsor. Once the IRB reviews and accepts that appropriate follow-up action has occurred, an official acknowledgement will be sent to the PI. The PI should file IRB acknowledgement with corresponding deviation documentation.

Protocol Exception Documentation and IRB Reporting

When a protocol exception is anticipated, the PI should promptly assess the impact the exception may have on the study or on the welfare of subjects, and make a determination as to whether the impact will be Minor or Significant. All protocol exceptions should be documented.

- It is up to the PI and research staff to determine a suitable method of documentation, such as a summary log (see EQuIP website for samples), or a note to be filed in the investigator's study records. Whatever method is determined, it must include the following information:
- Date or Time Frame of Proposed Exception
- Description of Protocol Exception
- Reason and Rationale of Proposed Exception
- Explanation why action will be one-time, rather than permanent
- PI assessment whether Minor or Significant, and reason for choice
- PI signature and date

If protocol exception is deemed Significant, the PI is required to submit the request to the IRB and receive approval **prior to implementation**. There is a significant exception request form that should be used available on the IRB website. If there is an outside study sponsor, obtain approval for the exception request (if applicable) prior to IRB submissions. Once the IRB reviews and approves the anticipated exception, the form will be signed and sent to the PI. The PI should file the IRB approval with corresponding exception documentation. Minor exceptions should be tracked and reported to the IRB at the next continuing renewal. All exceptions should be reported as appropriate to the sponsor, FDA and through the data and safety monitoring plan.

Notification To Subjects

When the IRB reviews the exceptions and deviations, a determination will be made as to whether information related to protocol changes should be provided to participants based on whether such information might relate to their willingness to continue to take part in the research. The investigator will be advised if subjects need to be informed.

Examples of Minor vs. Significant

When study deviations or exceptions are identified, it is the responsibility of the Principal Investigator to make an independent determination as to whether it should be classified as Minor or a Significant. Examples of common Protocol Deviations and Exceptions and how they may be classified are provided below. However, based on protocol specific details, sometimes what may be considered minor for one study may be significant in another. This is not an all-inclusive list of all potential events. Please contact the IRB office if there are questions.

Minor:

1. Missing signed informed consent document but the PI can verify by other methods consent was obtained
2. Inappropriate documentation of informed consent including
 - a. Missing signatures (other than subject and/or parent/legal guardian)
 - b. Copy of consent not given to subject
 - c. Wrong dates
 - d. Wrong signature lines
 - e. Missing documentation of relationship of person providing parental permission.) if relationship confirmed to be parent /guardian)
3. Use of invalid consent for a small number of subject as long as the content of the form contains all information that is included in the valid consent
4. Study visits/procedures that are either omitted, conducted outside the visit window or in a different sequence than specified in the protocol as long as this has not potentially impacted the safety and welfare of the subject.
5. Over enrollment of subjects in research that has produced additional data of potential scientific value
6. Study personnel involved in research without appropriate training
7. Use of recruitment materials and processes that include small modifications from those that are approved
8. Assent obtained but not appropriately documented,

Please note, for all these events a single or infrequent occurrence may be considered minor, however, if it is discovered these events have involved a majority of research subjects or the frequency is increasing, this may signify a more systemic problem with the conduct of the research and this could lead to reclassification of the events as Significant.

Significant

1. Failure to obtain informed consent prior to initiating research procedures
2. Informed consent obtained after research procedures are initiated
3. Performing study procedures not approved by the IRB unless to eliminate immediate potential harm to the subject
4. Failure to perform a test approved in the protocol that is important to subject safety or data integrity
5. Drug medication (dosing and dispensing) errors regardless of whether a subject was negatively impacted
6. Failure to follow data and safety monitoring plan
7. Failure to report a serious, unanticipated adverse event that is thought to be possibly or definitively related to research interventions
8. Use of a recruitment process not approved by IRB
9. Enrollment of new subjects after IRB approval has expired
10. Enrolling a subject that does not meet inclusion/exclusion criteria
11. Enrolling an incarcerated youth or a ward of state in a protocol not previously approved to include these populations
12. Parental permission granted by someone other than the parent or legal guardian
13. Assent not obtained when required by IRB
14. Verbal consent obtained when IRB requires written consent

Related Content

Document Attributes

Title	Modifications: Exceptions and Deviations		
Author	Susan Kornetsky	Dates Reviewed/ Revised	04/01/05
Reviewed/ Revised by	Susan Kornetsky		06/20/05
			05/04/07
			09/24/08
Copyright	©Children's Hospital Boston, 2012	Last Modified	03/19/2010
Approved	Susan Kornetsky Director of Clinical Research Compliance Carleen Brunelli, MBA, PhD Vice President for Research Administration		